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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, 2016

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)

Zernikedreef 9
2333 CK Leiden
The Netherlands
(Address of principal executive offices)

Smital Shah, Chief Financial Officer
Tel: +31 88 166 7000
sshah@proqr.com, Zernikedreef 9, 2333 CK 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: 23,346,856

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, 2016 of ProQR Therapeutics N.V. (the "2016 Form 20-F"). Unless the context specifically indicates otherwise, references in this 2016 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, 2016 and 2015, and for the years ended December 31, 2016, December 31, 2015 and December 31, 2014, included in the 2016 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 2016.

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, QR-313 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, QR-313 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

Not applicable.

Item 2: Offer Statistics 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. We derived the selected financial data from our consolidated audited financial statements 2012 through 2016.

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, 2016	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	1,828	3,235	313	116	23
Research and development costs	(31,923)	(23,401)	(10,267)	(2,569)	(285)
General and administrative costs	(9,478)	(6,837)	(6,507)	(786)	(157)
Operating result	**(39,573)**	**(27,003)**	**(16,461)**	**(3,239)**	**(419)**
Finance income and expense	470	6,171	4,334	(14)	1
Net loss (attributable to equity holders of the Company)	**(39,103)**	**(20,832)**	**(12,127)**	**(3,253)**	**(418)**
Other comprehensive income	(16)	1	—	—	—
Total comprehensive loss (attributable to equity holders of the Company)	**(39,119)**	**(20,831)**	**(12,127)**	**(3,253)**	**(418)**
Share information					
Weighted average number of shares outstanding	23,346,507	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	€ (1.68)	€ (0.89)	€ (1.09)	€ (0.59)	€ (0.17)

	As at December 31,				
	2016	2015	2014	2013	2012
	(€ in thousands)				
Statement of financial position data:					
Cash and cash equivalents	59,200	94,865	112,736	4,129	249
Total assets	65,543	100,109	115,247	4,504	338
Total liabilities	12,407	10,310	5,843	4,593	239
Total shareholders' equity	53,136	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 $ 1.0541 to € 1.00, the official exchange rate quoted by the European Central Bank at the close of business on December 31, 2016. As at March 10, 2017, the official exchange rate of Euro to U.S. dollars was $ 1.0606 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
2016	1.0541	1.1069	1.0364	1.1569
Month ended				
September 30, 2016	1.1161	1.1212	1.1146	1.1296
October 31, 2016	1.0946	1.1026	1.0872	1.1236
November 30, 2016	1.0635	1.0799	1.0548	1.1095
December 31, 2016	1.0541	1.0543	1.0364	1.0762
January 31, 2017	1.0755	1.0614	1.0385	1.0755
February 28, 2017	1.0597	1.0643	1.0513	1.0808

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 and epidermolysis bullosa (EB), QR-313. We have had significant operating losses since our inception. Our net losses for the years ended December 31, 2014, December 31, 2015 and December 31, 2016 were approximately € 12,127,000, € 20,832,000 and € 39,103,000 respectively. At December 31, 2016, we had an accumulated deficit of € 75,733,000. 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, QR-313 or any 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 our 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 any of our product candidates, 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, 2016, we had approximately € 59,200,000 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 through mid-2018. 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. 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 completed its first clinical trial. 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 our 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 the clinical trial for QR-010 and pre-clinical testing of our product candidates are not necessarily predictive of the results of our ongoing and planned clinical trials of our product candidates. 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 the clinical trial of QR-010 and pre-clinical testing 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 and early 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, 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 technologies are unproven and may not result in marketable products.

We plan to develop a pipeline of product candidates using our proprietary RNA 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. The mechanism of action of our compounds could be different from what we today hypothesize. Also, we may discover that the molecules we develop 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 technologies may demonstrate different chemical and pharmacological properties in humans than they do in laboratory studies or animals. Even if our product candidates 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 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. This 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 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 our 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 QR-110, or obtain such status for QR-313 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 and QR-110 for CF and LCA, respectively, 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 intend to seek Orphan Drug designation for QR-313 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, QR-110 and QR-313, 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 that any 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 have obtained fast track designation for QR-010 for CF. We intend to seek fast track designation for QR-110 and QR-313, 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 one or more 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 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 clinical investigators and 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 investigators or 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 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 Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving 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, 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 of 2010, 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
- 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 Massachusetts General Hospital, or MGH, to patent rights that relate to certain RNA targeting technologies for generating functional proteins. 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. For our LCA program we have a world-wide exclusive sublicensable and royalty-bearing license to patent rights owned by the Radboud University Medical Center, or Radboud, for the commercial exploitation of antisense oligonucleotides that cause exon skipping in CEP290 pre-mRNA. 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 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 and Radboud, as well as our other licensors, may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, MGH and Radboud, 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, the license agreements may not provide us with a complete freedom to operate in the respective fields, 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. 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 none 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 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 F508del mutation. Although we believe that the claims of this patent are not valid or infringed,

particularly in light of the U.S. Supreme Court decision regarding the patentability of naturally-occurring nucleic acids, the patent owner may nonetheless initiate litigation. In addition, we are aware of patent positions related to the use of antisense oligonucleotides in the treatment of LCA and DEB, for which we have initiated negotiations to enter into exclusive license agreements. We have not entered into such license agreements, and there can be no guarantee that we will enter into such agreements on these positions on commercially reasonable terms or at all. If we do not enter into such license agreements, the patent owner(s) may initiate litigation for potential patent infringement. 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 thus far unidentified 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 could 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, the Special 301 Report (April 2016) 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, Galapagos/AbbVie, Proteostasis, Corbus Pharmaceuticals, Spyryx Biosciences, Flatley Discovery Labs and various other 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. Competing programs include CFTR potentiators, CFTR correctors and drug candidates with other mechanisms of action that seek to address the underlying cause of CF. For example, Vertex's Orkambi, a combination of lumacaftor and ivacaftor, is approved for CF patients who are homozygous for the F508del mutation in the U.S. and European Union. Also novel CFTR modulators are being developed, mostly to be used as double and triple combinations. 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.

Currently no disease modifying treatment is available for the treatment of DEB, the indication we are currently pursuing with the development of QR-313. Over the last years, several companies and academic groups have focused on the development of DEB treatments, which ranged from improved wound healing to disease-modifying approaches such as autologous gene therapy. We believe, we are the only company developing a RNA modulation program for the potential treatment of DEB caused by COL7A1 exon 73 mutations. Competitors include Fibrocell Science developing an autologous fibroblast cell therapy for the treatment of DEB that is currently being studied in a phase I clinical trial.

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 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;
- 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 technology 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, and impose additional health policy reforms, any of which could negatively impact our business. 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.

The new Trump administration and the leadership of the Republican majority in the U.S. Congress have spoken of their desire to repeal the Affordable Care Act and may seek to modify, repeal, or otherwise invalidate all, or certain provisions of, the Act. There is significant uncertainty whether any major changes will occur. Any such changes will take time to unfold, and could have an impact on coverage and reimbursement for healthcare items and services covered by plans that were authorized by the Affordable Care Act. Such reforms could have an adverse effect on anticipated revenues from therapeutic candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop therapeutic candidates. However, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us. 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 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 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 Organization, Structure and Operations

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 or clinical data 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.

Our international operations subject us to various risks, and our failure to manage these risks could adversely affect our results of operations.

We face significant operational risks as a result of doing business internationally, such as:

- fluctuations in foreign currency exchange rates;
- potentially adverse and/or unexpected tax consequences, including penalties due to the failure of tax planning or due to the challenge by tax authorities on the basis of transfer pricing and liabilities imposed from inconsistent enforcement;
- potential changes to the accounting standards, which may influence our financial situation and results;
- becoming subject to the different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- reduced protection of, or significant difficulties in enforcing, intellectual property rights in certain countries;
- difficulties in attracting and retaining qualified personnel;
- restrictions imposed by local labor practices and laws on our business and operations, including unilateral cancellation or modification of contracts;
- rapid changes in global government, economic and political policies and conditions, political or civil unrest or instability, terrorism or epidemics and other similar outbreaks or events, and potential failure in confidence of our suppliers or customers due to such changes or events; and
- tariffs, trade protection measures, import or export licensing requirements, trade embargoes and other trade barriers.

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, 2016, we had approximately € 59,200,000 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.

We may be exposed to significant foreign exchange risk.

We incur portions of our expenses, and may in the future derive revenues, in currencies other than the euro, in particular, the U.S. dollar. As a result, we are exposed to foreign currency exchange risk as our results of operations and cash flows are subject to fluctuations in foreign currency exchange rates. We currently do not engage in hedging transactions to protect against uncertainty in future exchange rates between particular foreign currencies and the euro. Therefore, for example, an increase in the value of the U.S. dollar against the euro could be expected to have a negative impact on our expenditures, although we do match the currency of our cash and cash equivalents with expected cash out flows. We cannot predict the impact of foreign currency fluctuations, and foreign currency fluctuations in the future may adversely affect our financial condition, results of operations and cash flows.

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, 2016, we had a total of approximately € 82.9 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 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 $3.64 per share at the close of the trading on March 30, 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, the European Union and other jurisdictions;
- 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 by our existing shareholders in the public market could cause our share price to fall.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of our ordinary shares could decline. In addition, a substantial number of ordinary shares subject to outstanding options are or will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

If we sell shares of our common stock in future financings, stockholders may experience immediate dilution and, as a result, our stock price may decline.

We may from time to time issue additional shares of our common stock or securities convertible into our common stock, including in future financings that we may undertake. In October 2015, we filed a shelf registration statement on Form F-3, pursuant to which we may issue and sell ordinary shares, warrants and units (or any combination of the foregoing) in one or more transactions up to a maximum value of $200.0 million. In addition, in October 2015, we entered into an agreement for an at-the-market offering facility, or ATM facility, with Cantor Fitzgerald & Co., pursuant to which we may issue shares of our common stock from time to time under our shelf registration statement up to a maximum of $60.0 million. If we issue additional shares of our common stock or securities convertible into common stock, including pursuant to our shelf registration statement or our ATM facility, our stockholders may experience immediate dilution and, as a result, our stock price may decline.

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 members of our management board and supervisory

board 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 our Company;
- impeding a merger, consolidation, takeover or other business combination involving our Company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our Company.

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;
- 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 or suspended 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 (other than those which follow from Dutch law) 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.

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

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.

Our status as a PFIC 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 and may fluctuate considerably given that market prices of technology companies have been especially volatile. In addition, the composition of our income and assets will be affected by how, and how quickly, we spend our cash, including any cash raised pursuant to this offering. Based on the average value of our gross assets, we believe that we may be classified as a PFIC for the 2016 taxable year.

We do not currently intend to provide the information necessary for U.S. holders to make a "qualified electing fund," or QEF, election if we are treated as a PFIC for any taxable year, and prospective investors should assume that a QEF election will not be available.

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 genetic rare diseases (sometimes called orphan diseases) such as cystic fibrosis, Leber's congenital amaurosis Type 10 and dystrophic epidermolysis bullosa. Based on our unique proprietary RNA platform technologies we are growing our pipeline with patients and loved ones in mind.

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. Until December 31, 2016, 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 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 Zernikedreef 9, 2333 CK Leiden, the Netherlands, telephone number +31 88 166 7000. The name and address of our agent for service in the United States is CT 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 that discovers and develops RNA therapeutics for a better future for patients with severe genetic rare diseases. Our team of dedicated ProQRians works closely with patient groups and our academic partners and this has led to many successes in the short life-span of the company. Our lead program targets the most common mutation in CF and because of an aggressive and innovative development strategy positive data from a biomarker study in CF patients was presented in 2016. A second clinical trial in CF patients is ongoing and is expected to read out in mid-2017. Our first program targeting an inherited blindness is expected to enter clinical trials during the first half of 2017 and more programs in this therapeutic area are being advanced. The third area that we focus on are debilitating skin diseases, for which we are developing several programs. The first of these is expected to enter clinical trials in 2018. Our diversified pipeline that we presented during a Research & Development Day in 2016 is the result of our in-house discovery engine that we call the innovation unit. This group has been very productive in discovering new programs based upon our toolbox of RNA technologies that we have in-licensed or developed in-house. We currently have discovery programs including programs in Usher syndrome, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease, amyloid beta related disorders and Friedreich's ataxia. We believe our strong team, excellent partners and our extensive pipeline will lead to a sustainable future for our company and to accomplish our quest to make a meaningful impact on the lives of patients in need.

QR-010 and Cystic Fibrosis (CF)

CF is a genetic disease that causes early morbidity and mortality. CF currently has no cure. The median age of death for CF patients is 30 years or less, 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 F508del mutation that we are targeting is the most prevalent and is present in approximately 85% of all CF patients in the Western world and approximately 65,000 patients worldwide. 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, lung-damaging 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 targeting the mRNA defect encoded by the F508del mutation in the CFTR gene of CF patients and restoring CFTR function. 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 started two global clinical studies of QR-010 in 2015. During the North American Cystic Fibrosis conference (NACFC) from October 26 – 29, 2016 we presented positive results from PQ-010-002, a proof-of-concept trial demonstrating that QR-010 restores CFTR function in the nasal linings of patients that are homozygous (who carry two allelic copies) of the F508del mutation. CFTR is the protein channel that is defective in patients with CF, and presence or absence of function of CFTR can be measured by an important biomarker called the nasal potential difference, or NPD, assay. Following four weeks of topical therapy, QR-010 improved the CFTR-mediated total chloride response, a direct measure of CFTR function. This was confirmed by the restoration of other indicators of CFTR function, such as the sodium channel activity. In subjects that were compound heterozygous (who carry one copy of the F508del mutation and one other disease causing mutation), no meaningful difference was measured. QR-010 was observed to be well-tolerated in all subjects.

Besides the completed NPD trial, we are running a second clinical trial. This Phase 1b clinical trial, which we refer to as PQ-010-001, is a randomized, double-blind, placebo-controlled, 28-day dose-escalation trial that is being conducted in 27 sites in North America and Europe. The primary endpoint of the trial is to evaluate the safety, tolerability and pharmacokinetics, of single and multiple ascending doses of inhaled QR-010 in approximately 64 CF patients carrying two copies (homozygotes) of the F508del mutation. This trial will also assess a number of exploratory efficacy endpoints, although the trial is not powered for statistical significance on these endpoints. The single dose portion of the trial has been completed. No dose-limiting toxicity was observed up to the highest dose tested. We expect to report top-line data from the full trial in mid-2017.

In July 2016, QR-010 received Fast Track designation from the FDA for the treatment of patients with CF due to the F508del mutation. Fast Track designation is granted by the FDA to drugs that are under development for serious conditions and have the potential to fulfill an unmet medical need. It was established with the intention to bring promising drugs to patients sooner by facilitating the development with more frequent FDA interactions and expediting the review process.

QR-010 has been granted orphan drug designation in the United States and the European Union for CF. 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 Type 10 (LCA 10)

LCA is the most common genetic cause of blindness in childhood. LCA is caused by a genetic defect in 19 or more associated genes. Classification of LCA is based on the disease causing gene. The most frequently mutated LCA gene in LCA patients in North America and Europe is CEP290 that is associated with LCA Type 10 (LCA 10). 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 10 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 10 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 CEP290 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 10 provides support for the clinical development and therapeutic potential of QR-110. In studies conducted with QR-110 using relevant pre-clinical LCA 10 models, QR-110 was observed to restore CEP290 wild-type mRNA and protein levels. It was observed that QR-110 restored CEP290 mRNA and protein levels in primary LCA 10 fibroblasts from patients that are homozygous for the p.Cys998X mutation to approximately 100% of wild-type and to approximately 50% of wild-type in cells from compound heterozygous patients**.** It was also observed that QR-110 reaches the correct layer of the retina (the outer nuclear layer) after administration by intravitreal injections. In a 3D optic cup organoid model QR-110 showed restoration of CEP290 wild-type mRNA in a dose dependent manner. In the first half of 2017 we intend to start our first clinical trial directly in LCA 10 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.

QR-110 has been granted orphan drug designation in the United States and the European Union for LCA.

QR-313 and Dystrophic Epidermolysis Bullosa (DEB)

Dystrophic epidermolysis bullosa (DEB) is a genetic orphan disease of the skin and other mucosal membranes. The hallmark of the disease is severe blistering and poorly healing wounds that result from minimal pressure. Patients with the recessive form of DEB (RDEB) have a limited life expectancy and low quality of life. Patients with the dominant form (DDEB) have variable expression of the disease but is also associated with significant morbidity. There is currently no treatment for DEB. Aggressive and costly palliative care provided to these patients does not address the underlying cause of the disease. DEB is caused by mutations in the COL7A1 gene which leads to an absence of functional collagen type VII (C7) protein which is essential for formation of anchoring fibrils that link the epidermis to the dermis.

We are developing a single-stranded oligonucleotide, QR-313, for patients with DEB caused by mutations in a specific part of the COL7A1 gene called exon 73. QR-313 is designed to exclude exon 73 from the COL7A1 mRNA. Skipping of exon 73 leads to an mRNA that is translated into a truncated, but functional COL7A1 protein that is able to form anchoring fibrils that should improve the stability of the skin. There are multiple mutations associated with DEB, several of which lie within exon 73.

QR-313 is being formulated in a hydrogel that will be applied topically to existing wounds in patients with DEB. QR-313 is designed to restore functional COL7A1 protein with the aim to facilitate wound healing and protect against future blistering. In pre-clinical models skipping of exon 73 by QR-313 has been observed in a 3D human full thickness skin model. If this exon skipping approach is proven to be of benefit for DEB patients, there may be other COL7A1 mutations that can be targeted with an approach similar to QR-313.

Innovation pipeline

The innovation unit is our internal discovery engine, which we use to discover additional molecules through internal research and external collaborators. These pipeline programs are based on our multiple RNA technologies that were discovered internally or in-licensed. We have a rigorous evaluation process in identifying programs that are ready to leave the innovation unit and move into development. The criteria include established genetic causality, ability to deliver to the target organ, intellectual property protection, strong pre-clinical 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 Usher syndrome and Fuchs endothelial corneal dystrophy (FECD) both areas of ophthalmology with high unmet medical need. We further have programs in our central nervous system, or CNS, franchise for Huntington's disease and amyloid beta related disorders. In our neuromuscular franchise we have a program for Friedreich's ataxia.

Our Strategy

We are dedicated to improving the lives of patients and their loved ones through the development of RNA-therapies for severe genetic orphan diseases. We have an initial focus on patients with CF, LCA 10 and DEB. Key elements of our strategy include:

- ***Develop drugs for patients in need.*** Through our patient-centric approach we work to develop best-in-class therapies and to advance the understanding of conditions that we target. As RNA Therapies have become an established modality we are translating new applications in a pipeline of products for patients suffering from rare diseases. We believe this strategy enables us to build a sustainable independent business.
- ***Independently develop and commercialize 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 and a first clinical trial in CF patients. We believe these data support the potential of QR-010 as a disease-modifying therapy for CF patients. We are currently running a second global clinical trial of QR-010 that will enroll approximately 64 CF patients with two copies of the F508del mutation. Top-line data is expected in mid-2017. We are studying applications of RNA technologies for CF mutations other than F508del. We intend to commercialize QR-010 ourselves, if approved, and retain all commercial rights in major markets.

- ***Rapidly advance our ophthalmology franchise, including QR-110 for the treatment of LCA 10.*** 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 10, 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 2016 and expect to start our first clinical trial in LCA 10 patients in the first half of 2017.
- ***Utilize our proprietary RNA 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.
- ***Leverage our pipeline through considering out-licensing, spinouts or collaborative partnerships.*** We plan to continue to advance the programs and technologies 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, out-licensing or collaborative partnerships with pharmaceutical companies. These partnerships may provide us with further validation of our approach, 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 target defective mRNA in order to restore protein functionality. Our goal to restore translation of functional proteins is unlike other approaches in the RNA therapeutics field, such as RNAi and antisense that use RNA molecules to downregulate genes. Our molecules are 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. 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.

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 scientific experts and thought leaders 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

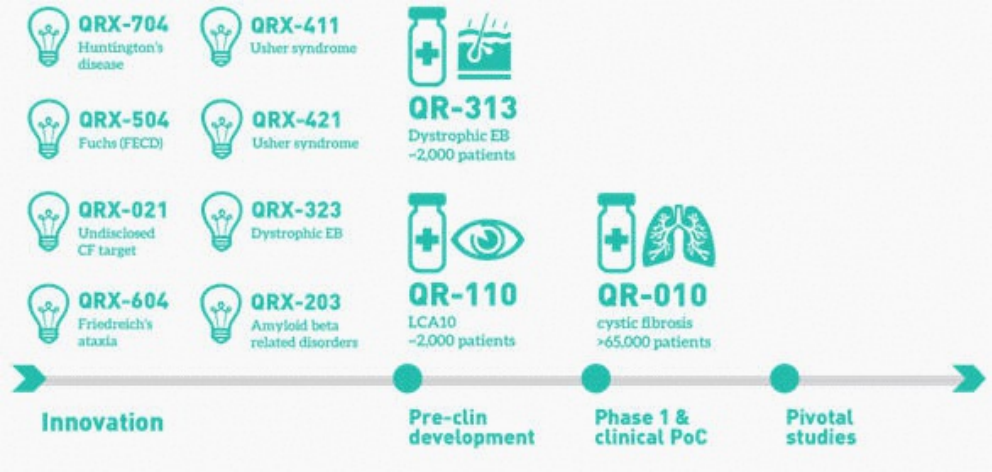
✓ Well understood relationship between the genetic defect and the disease manifestations

✓ 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:

Program pipeline



Patient Centric Approach

ProQR aims to develop best-in-class therapies as well as to improve patient care through awareness, education, and advancing the understanding of conditions that we target. In order to achieve this goal, ProQR strives to integrate the patient voice into our decision-making throughout the drug development process. Because we believe that a patient-centric strategy is crucial to our success, we have established the Patient and Medical Community Engagement (PMCE) team. This dedicated team's purpose is to listen to and represent the patient voice internally as well as to collaborate externally with the communities we serve.

Cystic Fibrosis

Cystic Fibrosis Background

CF is the most common fatal inherited disease in the Western world and affects an approximately 65,000 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 illustrates a defective CFTR protein hampering the efflux of chloride in lung epithelial cells.

Chloride ion flow by wild-type CFTR and F508del 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 is 30 years or less.

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 85% of CF patients in the Western world are affected by the F508del mutation. Of which approximately 45% are homozygous for the F508del mutation and approximately 40% are compound heterozygous for the F508del mutation.

In the F508del 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.

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 30 years or less.

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 30 years or less, 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-F508del 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 F508del mutation affects approximately 85% of CF patients in the Western world. Unlike the "gating" mutations, F508del is a "processing" mutation, and as such, CFTR with the F508del mutation is not expressed at the cell surface and cannot be potentiated by small potentiating molecules like Kalydeco.

Potentiator/corrector combination for F508del mutations

For patients aged 6 years and above and homozygous for the F508del mutation, Vertex Pharmaceuticals has received regulatory approval for Orkambi. 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 F508del CFTR 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 many homozygous F508del 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 12,000 US patients could be treated with Orkambi at an estimated annual cost of approximately $260,000 in addition to the cost of standard of care. We believe these studies validate that F508del 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 RNA Approach

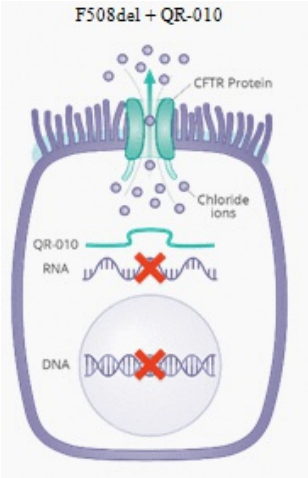
QR-010 is a first-in-class RNA oligonucleotide designed to address the underlying cause of the disease by targeting the mRNA in CF patients that have the F508del mutation. QR-010 is designed to bind to the defective CFTR mRNA and restore CFTR function. We believe we are currently the only company pursuing this novel approach for CF patients.

QR-010 for Treatment of CF

We are developing QR-010 as an inhaled treatment for CF patients. QR-010 is a single stranded RNA oligonucleotide designed to restore CFTR function in CF patients with the F508del gene mutation. QR-010 is 33 nucleotides long and is designed to bind to the CFTR mRNA sequences that are adjacent to the deleted F508del region of the mRNA.

The figure below represents, from left to right, wild-type CFTR function in a normal cell, impaired CFTR function in a cell with a F508del mutation and a F508del mutated cell treated with QR-010, which would be expected to result in restoration of chloride efflux.

Chloride ion flow: restoration through QR-010 treatment



Clinical Development for QR-010

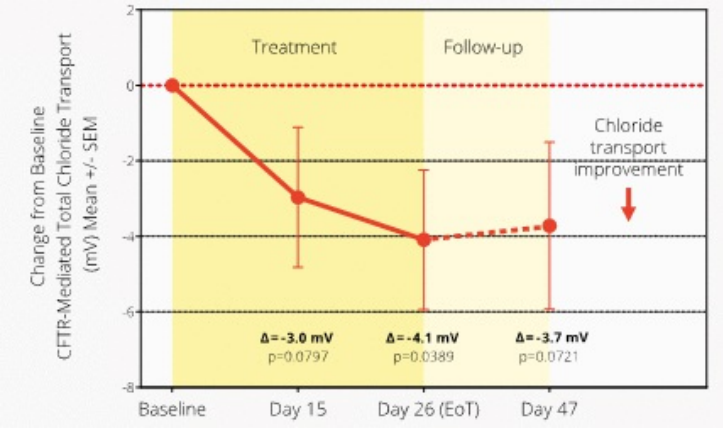
We conducted two clinical trials of QR-010 in parallel. Study PQ-010-002 is a proof-of-concept trial evaluating topical administration of QR-010 and its effect on the nasal potential difference (NPD), a biomarker of CFTR function. This trial opened for enrollment in September 2015 and was completed in September 2016. Study PQ-010-001 is a Phase 1b safety and tolerability trial. This trial opened for enrollment in June 2015 and is currently enrolling.

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 pre-clinical animal models and in CF patients. Our trial was designed to investigate the ability of QR-010 to restore CFTR function in patients. Restoration of CFTR function has been observed in pre-clinical NPD studies using mouse models. The primary outcome measure was to determine the effect of topical administration of QR-010 to the nasal mucosa on the restoration of CFTR-mediated chloride transport as measured by NPD in CF patients with the F508del CFTR mutation. Secondary endpoints included maximal basal potential difference reflecting sodium channel activity. Nasal administration is not the intended route of administration 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. All subjects were adults over 18 years old with CF either homozygous for the F508del mutation or compound heterozygotes with one copy of the F508del mutation and one copy of another disease causing mutation. The trial was conducted in five sites in the U.S., France and Belgium. QR-010 was administered intranasal 5 mg in each nostril 3 times weekly for 4 weeks (12 doses). The NPD measurements were done at baseline, after 6 doses (Day 15), after 11 doses (Day 26) and 21 days after the last dose (Day 47).

Topline results were reported at the North American CF Conference (Sermet-Gaudulus, Pediatr Pulmonol 2016 Suppl 45:485) in October 2016. In the per-protocol population of subjects homozygous for the F508del mutation meeting the pre-specified inclusion criteria (n=7), the average change from baseline in NPD at day 26 was statistically significant, -4.1 mV (p=0.0389). This finding was supported by a change in sodium channel activity (specifically, a measure called max basal potential difference, or PD) and other sensitivity analyses of the NPD measurements, all pointing to strong evidence of restoration of CFTR activity. In subjects compound heterozygous for the F508del mutation, the average change from baseline in NPD was not significantly different at day 26. A responder analysis of individual subjects assessing the impact of the second mutation is currently ongoing. QR-010 administered via the intranasal route was observed to be well tolerated.

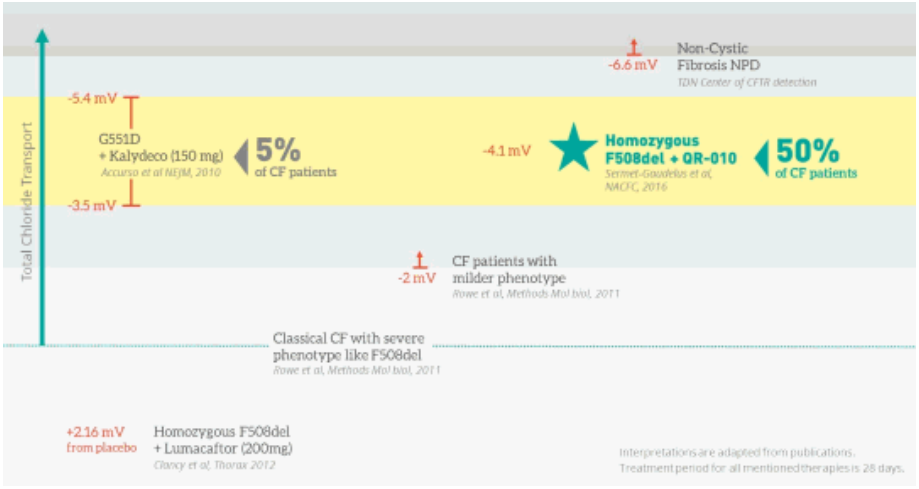
QR-010 improves CFTR function in F508del homozygous CF patients as measured by NPD



N= 7 (per protocol population). Parameter = within subject change from baseline in Cl-free+iso. Average both nostrils. Baseline = average of 2 most recent pre-dose assessments. P = one-sided 5% paired t-test.

We observed from the results of this trial that QR-010 improved CFTR function in homozygous F508del patients as evidenced by both the increase in CFTR activity measured in the CFTR-mediated total chloride response and the decrease in sodium channel activity as measured by the max basal potential difference. The magnitude of the change observed in this trial is similar to that published for other commercially available treatment in CF patients with the G551D mutation and superior to data published for lumacaftor in patients with the F508del mutation.

Putting QR-010 clinical NPD results in perspective



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

This 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. The trial includes CF patients that are homozygous for F508del and age 18 years and above. The trial is being conducted at 27 sites in North America and select EU countries and will enroll approximately 64 patients. The trial consists of 4 cohorts of ascending single dosed and 4 cohorts of ascending multiples doses (12 doses over 4 weeks). In each cohort, randomization is 3:1, meaning that 6 patients will receive QR-010 and 2 patients will receive placebo.

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. The primary outcome measures are to characterize safety, tolerability and pharmacokinetics of QR-010 in CF patients. Pharmacokinetics will be assessed in serum, urine and sputum. These measurements will allow us to establish the safety for QR-010 as well as give indications of uptake into the lung and systemic circulation in order to provide PK/PD information to design our future trials. 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. In October 2016, we reported that the single dose portion of the trial consisting of 4 cohorts has been completed. No dose-limiting toxicity was observed up to the highest dose tested. The dose escalating multiple-dose trial (12 doses administered over 4 weeks) is currently enrolling cohort 7 and topline results are expected to be available in mid-2017. Further update on enrollment will be provided at the European Cystic Fibrosis Conference (ECFS).

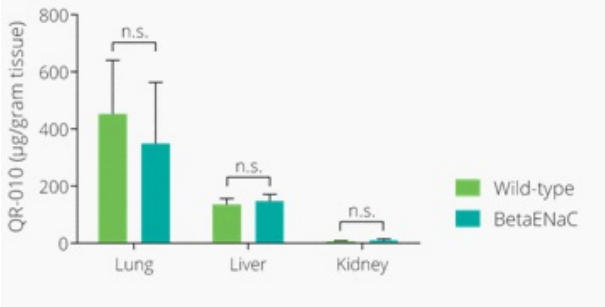
PQ-010-003 Phase 2 Trial

PQ-001-003 is currently planned as a Phase 2 multicenter, randomized, double-blind, placebo-controlled 12-week trial to evaluate the safety, efficacy, and pharmacokinetics of QR-010 in cystic fibrosis subjects with the F508del mutation. The trial will be conducted at clinical centers in North America, EU and possibly other countries. We anticipate to begin recruitment for this trial in 2018.

Inhaled administration of QR-010

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 F508del 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.

Bio-distribution of QR-010 to organs in wild-type and CF-like lung phenotype



Pre-clinical evidence for QR-010

As shown in the figure, 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.

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 F508del 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 F508del mutation. Most notably, and distinct from other molecules in development for CFTR mutation specific molecules, in two independent *in vivo* activity assays in F508del-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 F508del-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.

Research Grants

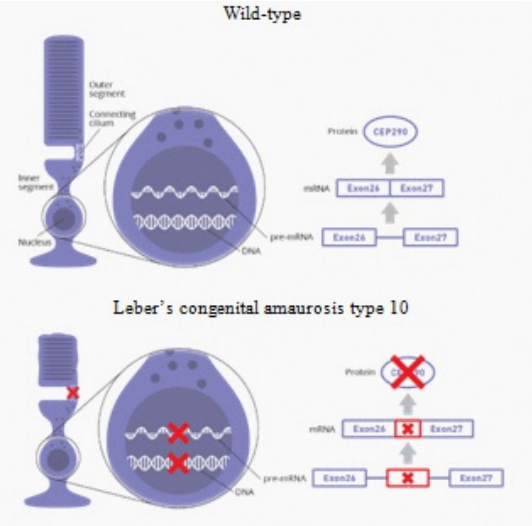
In August 2014, we entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide us with up to $ 3 million to support the clinical development of QR-010. In 2015, the Company and its academic 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. In 2016, ProQR also received additional tranches totaling €0.4 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 cause of 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 disease phenotype (LCA 10). Patients affected by this mutation typically lose sight in the first years of life. In LCA 10 patients, this mutation leads to significant decrease in CEP290 protein within the photoreceptor cells in the retina. Clinical features of CEP290-mediated LCA include loss of vision, involuntary eye movement or nystagmus, abnormalities of pupil reactions and no detectable photoreceptor electrical signals on electroretinography (ERG).

Representation of the p.Cys998X mutation causing LCA 10



LCA Genetics

The p.Cys998X mutation is a single nucleotide substitution in the CEP290 gene that creates a new splice site, also called a cryptic splice 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 of the cell. When CEP290 is absent, there is a disturbance in normal protein transport to the outer segments which provokes the shortening of the outer segment and its inability to perform its light transducing function.

LCA Prevalence and Diagnosis

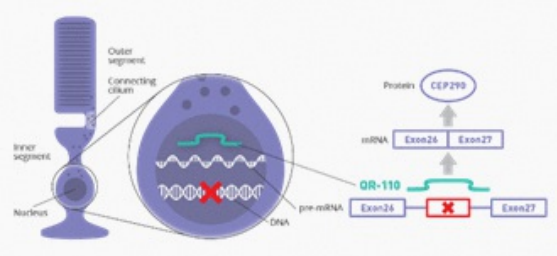
LCA is caused by a genetic defect in 20 or more associated genes. The most common mutation is the p.Cys998X in the CEP290 gene causing LCA 10. Although diagnosis rates vary, our estimations indicate this mutation to occur in approximately 2,000 patients in the Western world.

Patients are initially diagnosed through the presence of clinical symptoms. Nystagmus, rapid involuntary movements of the eyes, tends to be the first symptom visible as well as oculo-digital signs comprising eye poking, pressing, and rubbing, 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 confirm the diagnosis and determine the type of LCA in order 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 10

There are currently no disease modifying treatments approved or potential treatments in clinical trials for patients with p.Cys998X associated LCA 10, a form of LCA. There are other approaches in pre-clinical development for the p.Cys998X mutation that target the disease at the DNA level. 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.

QR-110 for LCA 10, splice correction for p.Cys998X CEP290 mRNA



QR-110 binds to pre-mRNA and silences the cryptic splice site leading to production of normal mRNA

QR-110 for the treatment of LCA 10

Our lead product candidate in the LCA 10 space, QR-110, is a first-in-class single stranded RNA oligonucleotide of 17 nucleotides long. It is designed to treat the disease by binding to the pre-mRNA and thereby silencing the cryptic splice site caused by the p.Cys998X mutation. 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. The intended route of delivery is through intravitreal injection.

Clinical Development for QR-110

We believe the activity seen in our pre-clinical models of LCA 10 provides strong support for the clinical development and therapeutic potential of QR-110. Currently, we are finalizing pre-clinical good laboratory practice, or GLP, safety studies and work to start our first clinical trial in LCA 10 patients.

We expect to commence clinical development of QR-110 in the first half of 2017 with the initiation of a Phase 1b/2 clinical trial. This trial is an open label trial evaluating multiple doses of QR-110 at different dose levels. Eligible subjects will be LCA 10 patients that are homozygous or compound heterozygous for the p.Cys998X mutation. The primary objective will be to evaluate the safety and tolerability of QR-110 administered via intravitreal injection in subjects with LCA 10 due to the p.Cys998X mutation. Secondary objectives will include the assessment of pharmacokinetics and efficacy as assessed by specialized ophthalmic tests.

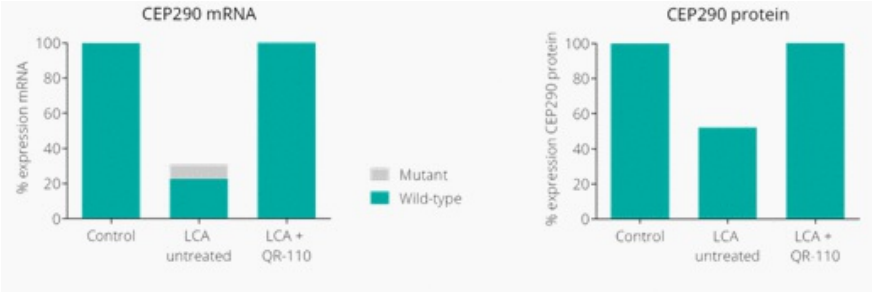
Pre-clinical evidence for QR-110

We have conducted in vitro and in vivo pre-clinical studies that we believe support the clinical development to explore the therapeutic potential of QR-110.

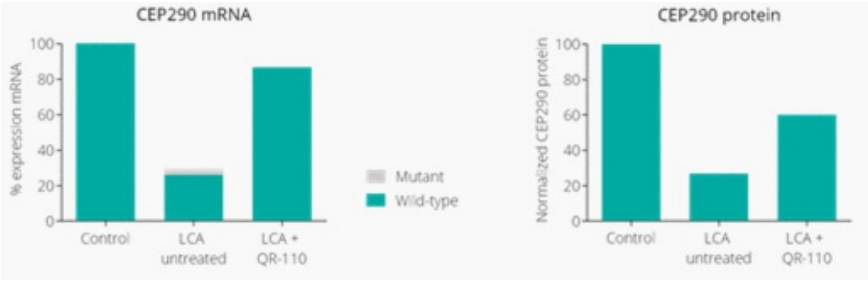
QR-110 assessment in patient fibroblasts

Since QR-110 targets the splicing process, the most direct measurable outcome of activity is the profiling and quantification of CEP290 transcripts (wild-type and mutant) and protein before and after treatment. In pre-clinical studies to date, QR-110 has demonstrated restoration of CEP290 wild-type (correctly spliced) mRNA and protein in cultured fibroblast cells of LCA 10 patients homozygous and compound heterozygous for the p.Cys998X mutation.

Homozygous cells (p.Cys998X/p.Cys998X; LFB-3) (figure A)



Compound heterozygous cells (p.Cys998X/p.Lys1575X; LFB-6) (figure B)



Effect of QR-110 at the mRNA and protein level in fibroblast cells from LCA 10 patients that are A) homozygous and B) compound heterozygous for the p.Cys998X mutation. Normalized wild-type and mutant CEP290 mRNA expression (copies/ng) after transfection of LCA 10 fibroblasts with QR-110, analyzed with one-step ddPCR. For protein data (Western Blot), expression is shown relative to control cells without the mutation. Error bars show mean with SEM. *p<0.05, **p<0.01, ***p<0.001, vs. mock treated cells, Student's t-test.

The figure above summarizes the observations from our pre-clinical data that treatment with QR-110 may be able to increase the expression of wild-type CEP290 mRNA and protein in fibroblast cells from LCA 10 patient that are homozygous for the p.Cys998X mutation. Furthermore, we observed that treatment with QR-110 resulted in a decrease in levels of mutant mRNA (figure A, left and center). The mRNA and protein profile restoration trend is also observed in LCA 10 fibroblasts that are compound heterozygous for the p.Cys998X mutation (figure B, left and center).

Changes in the mRNA profile are supported by a wild-type CEP290 protein increase illustrated by Western blot. Results demonstrate that in LCA 10 fibroblasts that are homozygous for the p.Cys998X mutation, in vitro treatment with QR-110 restored CEP290 protein levels to that of control cells (figure A, right panel). In LCA 10 fibroblast that are compound heterozygous for the p.Cys998X mutation, QR-110 treatment in vitro restored CEP290 protein levels to ~50% of control cells (figure B, right panel). This is expected since in these compound heterozygous cells only one mutated allele carries the p.Cys998X mutation and therefore only one allele can be targeted by QR-110 treatment. It is worth it to point out that patients that are heterozygous for the p.Cys998X mutation, with one normal allele and one allele carrying the p.Cys998X mutation, are asymptomatic. This indicates that correction of one diseased allele could be enough to prevent or stop progression of the disease.

QR-110 activity in optic cup model

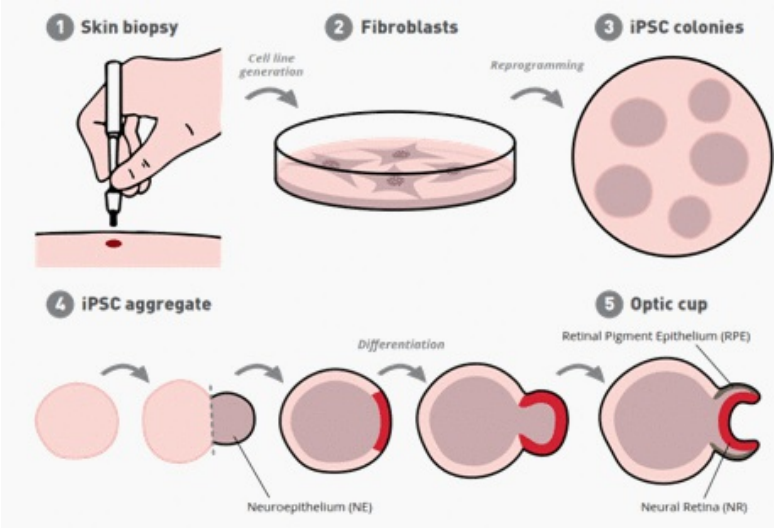
Optic cups are a retinal organoid model derived from fibroblasts of a LCA 10 patient harvested through skin biopsies. The cells are reprogrammed into induced pluripotent stem cells, or iPSC, and later differentiated into retinal pigmented epithelium cells and neural retinal cells, also known as three-dimensional optic cups.

Optic cups constitute a convenient and clinically relevant model system to thoroughly study the mechanisms of inherited retinal degeneration since, unlike the classic cell models, these 3D organoids simulate the disease phenotype and provide an appropriate cellular model with the genetic mutations in genomic context.

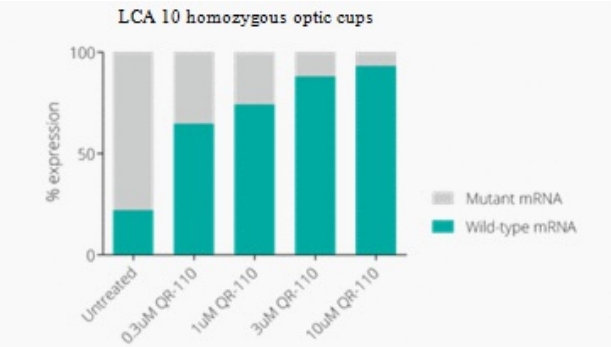
The clinical and molecular relevance of the optic cup model, coupled with the absence of an animal model, makes the optic cup the best model in which to simulate the mechanisms of CEP290 LCA and effectively test the potential of QR-110.

LCA 10 patient derived optic cups were exposed to QR-110. First, we observed from the results that QR-110 is able to enter the cells without use of any transfection agents. Second, QR-110 elicited a dose-dependent restoration of CEP290 wild-type mRNA expression. And third, increased CEP290 mRNA expression was also associated with a commensurate decrease in mutant CEP290 mRNA.

Generation of LCA 10 patient iPSC-derived optic cups



QR-110 increases wild-type CEP290 mRNA levels in a dose-dependent manner in LCA 10 optic cups

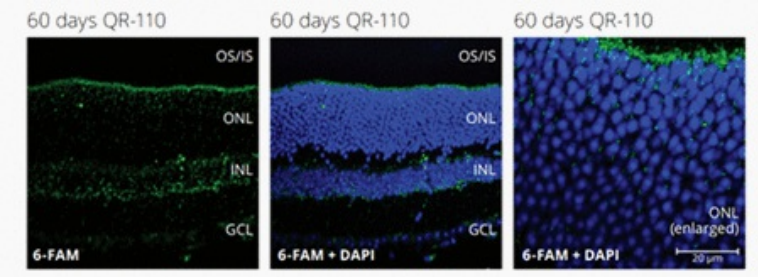


LCA 10 p.Cys998X homozygous patient fibroblasts were reprogrammed into iPSC which were differentiated into optic cups for 96 days and treated with different amounts of QR-110 for another 28 days (Parfitt et al. 2016) and analyzed using end-point PCR.

Retinal Distribution of QR-110

Labelled QR-110 (green) administered via intravitreal injection into wild-type mice eyes. We demonstrated that QR-110 enters the target cells of the retina, including the photoreceptor cells. QR-110 was detected 60 days (the maximum time point tested) following a single injection.

QR-110 reaches target cells after intravitreal injection



Retinal distribution of 6FAM-labelled QR-110 following single intravitreal injection of 100 µg in wild-type mice.

Dystrophic Epidermolysis Bullosa

DEB Background

Epidermolysis bullosa (EB) is a rare genetic disorder, primarily manifesting as a debilitating disease of the skin and mucosal membranes. It is characterized by mechanical fragility of epithelial tissues, blister formation, scarring and, in some subtypes, involvement of multiple other organs. EB is classified into four main subtypes, namely EB simplex (EBS), junctional EB (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler Syndrome (KS). The four main EB subtypes are distinguished by the level of the skin at which blisters develop.

In DEB the outer layer of the skin, the epidermis, separates from the inner layer, the dermis. This separation renders the skin fragile and causes severe blistering and scarring. All mucosal membranes are affected in DEB, therefore blistering is not limited to the skin, but is also present in the mouth, esophagus and downstream intestines.

DEB is usually a chronic, seriously debilitating disease with a shortened life expectancy due to malnutrition, infections, and malignancies.

DEB Genetics

The disease is caused by mutations in the COL7A1 gene. This gene is responsible for the production of a protein called collagen type VII (also referred to as C7), which is a major component of the anchoring fibril located below the basement membrane in the upper dermis that normally links the epidermis and the dermis together. DEB causing mutations occur more often in certain parts of the gene. One of those parts is exon 73.

DEB Prevalence and Diagnosis

DEB is a genetic disease that in some cases is inherited as an autosomal dominant (DDEB) and in others as an autosomal recessive trait (RDEB). The prevalence of DEB could differ across countries due to founder effects and differences in ethnic composition. While spatial variations, compounded with the scarcity of available data, make accurate calculations difficult, the estimated number of DEB patients in the western world is approximately 6,000 of which approximately 2,000 have mutations in exon 73.

Diagnostic testing for DEB is based the identification of the level of skin cleavage via immunofluorescence antigen mapping with C7 specific antibodies and/or determination of anchoring fibrils using transmission electron microscopy on, preferably, newly formed blisters.

Approaches for the Treatment of DEB

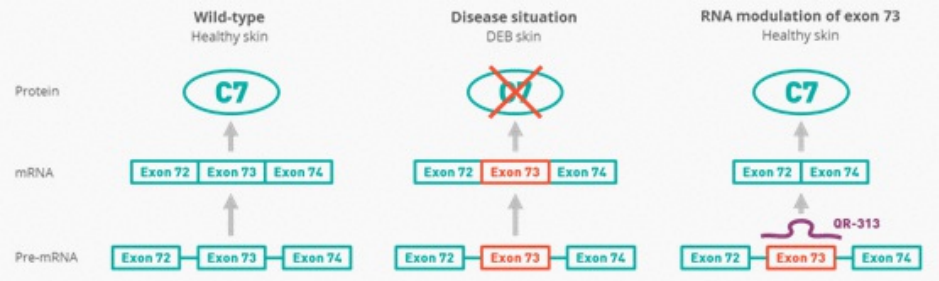
Currently no disease modifying treatment is available for DEB. Palliative treatment is the only treatment available for DEB patients and constitutes a time-consuming daily activity. Palliative treatment primarily consists of 1) treatment of (new) blisters by puncturing and draining blisters to prevent further spread from fluid pressure, 2) wound management to prevent infections, 3) prevention of skin trauma to avoid new blister formation, and 4) pain and itch relief.

QR-313 for the treatment of DEB

QR-313 is designed to specifically target mutations in exon 73 of the COL7A1 gene. QR-313 binds to a specific sequence in the COL7A1 pre-mRNA, thereby excluding exon 73 from the mature mRNA. This leads to a shortened version of the C7 protein that is functional in the formation of anchoring fibrils.

Because of the exon skipping approach, QR-313 is not specific to a single mutation but instead targets any mutation contained in exon 73.

Functional C7 protein: Restoration through QR-313 Treatment



Schematic shows pathway for generation of C7 protein in the healthy and disease situations (left and center diagrams, respectively). Hybridization of QR-313 to a specific sequence in COL7A1 pre-mRNA results in the exclusion of exon 73 from the mRNA, which leads to the production of a truncated but still functional C7 protein (right diagram).

Pre-clinical evidence for QR-313

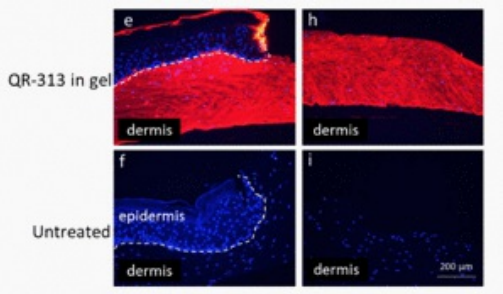
Clinical development of QR-313 focusses on topical delivery in the wounded skin of patients, with the aim of improved wound healing and reduced skin fragility. Therefore we aim to formulate QR-313 into a hydrogel for wound application that can be incorporated in the standard of care of patients.

Activity of QR-313 after topical application on human skin equivalents

In order to investigate topical delivery and exon skip potential of QR-313 we used Human Skin Equivalents, or HSEs. HSEs are an often used model to mimic the human skin. They are composed of both a dermal layer containing fibroblasts and an epidermal layer containing keratinocytes. The keratinocytes are fully differentiated to form all the different layers in the epidermis, including the stratum corneum. The culturing of HSEs is done at the air-liquid interface and therefore mimics the human situation. Moreover, by removing the epidermis from a portion of the skin equivalent, the blister phenotype of DEB can be modeled.

Cy5-labeled QR-313 in a hydrogel formulation was used in HSEs where a DEB blister was mimicked by removal of part of the epidermis. The figure below shows that diffusion of QR-313 into the dermis was observed both in the middle of the blister (blister bed) and at the edge of the blister (blister edge). QR-313 is not able to penetrate intact HSEs, and ex vivo skin (not shown).

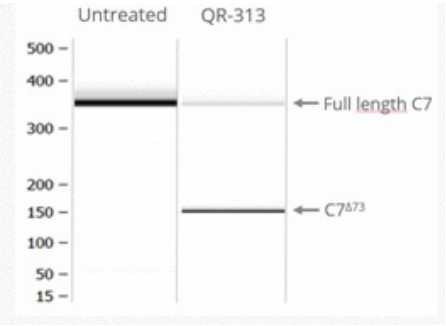
Delivery of Cy5-Labeled QR-313 Formulated in a Hydrogel



After 24 hour treatment (indicated at left of picture rows), HSE pieces (indicated at top of picture columns) were analyzed. QR-313 is depicted in red, nuclei are depicted in blue. White dotted line represents border between epidermis and dermis.

To examine the ability of QR-313 to induce exon skipping in dermal fibroblasts, we separated the epidermis from the dermis from the 24-hours incubated HSEs. RNA isolation was performed and analyzed for exclusion of exon 73 using RT-PCR. Exon 73 exclusion from the COL7A1 mRNA was observed in dermal cells treated with QR-313 formulated in a hydrogel. This shows that upon local application QR-313 is active in this model that mimics blistered EB skin.

QR-313 Induced Skipping of Exon 73 in C7 mRNA



Splicing products of COL7A1 mRNA either untreated or following treatment with Cy5-labeled QR-313 formulated in a hydrogel. RNA was isolated from treated HSEs (indicated at top of columns) and RT-PCR analysis was performed. The different COL7A1 mRNA products were analyzed for length. The 350 bp fragment represents the wild-type, full length amplicon including exon 73 mRNA while the 150 bp nucleotide fragment represents the modified Δ73 mRNA product.

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 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, LCA 10 and DEB. 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 F508del 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. Besides our LCA 10 program that we intend to take into clinical development in 2017, we have several discovery stage programs, including two programs targeting Usher syndrome and a program targeting 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. 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 two programs, called QRX-411 & QRX-421, we aim to target genetic alterations in the USH2A gene that lead to this vision loss. QRX-411 targets the frequent deep-intronic c.7595-2144A>G mutation that causes the inclusion of a pseudoexon in the mRNA disrupting the function of the protein. QRX-411 is designed to target the pre-mRNA and restore a wild-type sequence in the mRNA leading to wild-type mRNA and functional USH2A protein. QRX-421 targets mutations in exon 13 of the USH2A gene by skipping exon 13 from the mRNA restoring the reading frame and producing a truncated but functional protein. Both QRX-411 and QRX-421 are single-stranded RNA oligonucleotides intended to be administered 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, is a single-stranded RNA oligonucleotide that aims to prevent the buildup of RNA-protein foci that cause the corneal dystrophy in patients with expansion repeat mutation in the TCF4 gene.

Dermatology

Our product candidate, QR-313 targeting DEB caused by mutations in exon 73 has been moved into clinical development. If the exon skipping approach is proven to be of benefit for DEB patients, there may be other COL7A1 mutations that can be targeted with an exon skipping approach similar to QR-313.

CNS

In our CNS group we are working on product candidates for several disease targets, including a wide range of neuronal and cerebrovascular related amyloid beta disorders and Huntington's disease, or HD.

Amyloid beta, or Aß is a highly toxic and aggregate-prone family of peptides that are appears crucially involved in Alzheimer's disease, or AD, cerebral amyloid angiopathy, or CAA, and its familial form hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D). We are developing QRX-203, a RNA modulation therapy for Aß-induced amyloidosis. Using antisense oligonucleotide mediated exon skipping, we believe QRX-203 may prevent the translation of the amyloid region into its precursor protein APP. We believe this approach renders the release and aggregation of Aß impossible and may ultimately prevent the onset and/or or slow the progression of disease.

HD is an inherited progressive neurodegenerative disease, and one of the most common genetic disorders, with symptoms including involuntary movements, incoordination, impaired speech, cognitive decline, and depression. Individuals with HD have shortened life expectancy, and there is currently no disease-modifying treatment available. The disease is caused by an expanded repeat of CAG nucleotides in the Huntingtin, or HTT, gene, resulting in a mutated Huntingtin protein. When the mutated protein is present in the cells, small polyglutamine-containing protein fragments are formed. These fragments stick to each other, and accumulate in nerve cells, interfering with normal cellular functions, eventually leading to cell death. QRX-704 is an oligonucleotide based approach that is aimed to modify the HTT mRNA to prevent the formation of the toxic fragments, while the Huntingtin protein remains functional.

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 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 the welfare of animals and humans participating in our pre-clinical and clinical studies for reasons of ethics, quality, reliability and applicability of scientific studies. For conducting high quality (scientific) animal research, animal welfare is a prerequisite. By actively pursuing the 3R principles (Reduce, Refine and Replace), we are committed to minimalizing the number of animals needed, minimizing discomfort and pain of animals used and to using alternatives to animal research whenever possible in research and in the obligatory animal studies. All our current studies are approved by the (institutional or national) animal care and use committees.

Our aim is to monitor continually that animal experiments will be performed only if there are no viable or legal alternatives. Additionally, case by case, it will be evaluated if advances can be made in study designs (such as by ex-vivo studies or by conduction of small pilot studies first), or by using new technologies to achieve adequate statistical power without increasing the number of animals, combining studies, and improving use of toxicokinetic data to optimize dose selection.

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. CRO facilities are audited in person prior contracting. The housing, husbandry and animal welfare 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.

In 2015 we became part of an interdisciplinary consortium with Utrecht University (Faculty of Veterinary medicine and Ethics Institute), Radboud University (Medical Center, SYRCLE) and another private company, partly financed by The Netherlands Organization for Scientific Research, Responsible Innovation grant. The project proposes a more integrated approach towards innovation in the field of animal testing and focuses on translational strategies. ProQR is involved in the part of the project that aims to deliver step stones for practical guidelines to build robust translational strategies, to design innovative experiments (including animal models) for cystic fibrosis and develop a translational strategy for CF as a showcase.

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 delays in granting marketing approval for a patented active ingredient or use of an active ingredient. In Europe, a similar mechanism is available, such that patents may be eligible for a supplementary protection certificate to compensate for the time lost in obtaining marketing authorization for the active ingredient.

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, Japan, Mexico, New Zealand, Russia, South Africa and South Korea relating to certain aspects of our RNA targeting technology platform, including method of use claims relating to the use of single stranded oligonucleotides, particularly modified RNA oligonucleotides, for targeting RNA molecules in a living cell, as well as composition of matter claims relating to our QR-010 product candidate. In April 2016 the European equivalent in this patent family was granted by the European Patent Office, and the patent (EP 2852668 B1) was subsequently validated in all European Patent Convention contracting states. No opposition was filed after the 9-month opposition period. The U.S. patent application was granted on March 28, 2017 (US 9,605,255). The term of these EP and US patents and any patents resulting from the other applications in the patent family, if issued, would be expected to extend to at least 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 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 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 continuation application in which we have been pursuing composition of matter claims relating to QR-010. This application was allowed in December 2016. The term of the patent resulting from this allowed application is expected to extend to at least March 2025.

Patent Rights Relating to Our LCA Program

With regard to our LCA Program and our lead candidate in the LCA space, QR-110, we entered into an exclusive license agreement with the Radboud University Medical Center, Nijmegen, the Netherlands in April 2014 to obtain rights in a patent family with composition of matters claims directed to 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 at least 2032.

In February 2016, to further strengthen our position on QR-110, we filed our own international patent application to obtain intellectual property rights to a variety of improved antisense oligonucleotides and the use thereof in the treatment of LCA. This international patent application is expected to be continued in national and regional patent applications in August 2017. The term of any patents resulting from these applications, if issued, would be expected to extend to at least 2036.

Patent Rights Relating to Our DEB Program

With regard to our DEB program and our lead candidate in the DEB space, QR-313, we filed two international patent applications in March and May 2016 respectively, and that are expected to be continued in national and regional patent applications in September and November 2017 respectively. The term of any patents resulting from these applications, if issued, would be expected to extend to at least 2036.

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.

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 and milestones to MGH. We are also obligated to pay MGH up to $ 700,000 in additional 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. We have the first right to protect the licensed patent rights from alleged infringement. If we do not prosecute the alleged infringement, MGH may, at its own expense, initiate legal proceedings against the alleged infringer. We may 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, ProQR Therapeutics entered into an agreement with Leiden University Medical Center (LUMC) which gives the Company a world-wide, exclusive, royalty-bearing license in the field of amyloid beta related diseases, notably Alzheimer's disease and HCHWA-D, 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.

On January 24, 2017, ProQR Therapeutics entered into an agreement with LUMC, which gives the Company a world-wide, exclusive, royalty-bearing license in the field of Huntington'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 the HD program.

Manufacturing and Supply

We do not currently own or operate manufacturing facilities for the production of pre-clinical, clinical or commercial quantities of any of our product candidates. We currently contract with drug product formulation manufacturers for the production of QR-010 solution for nebulization, QR-110 solution for intravitreal injection, and QR-313 drug product and we expect to continue to do so to meet the pre-clinical 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, amongst others. The contract manufacturing organizations we use manufacture 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, Galapagos/AbbVie, Proteostasis, Corbus, Spyryx Biosciences, Flatley Discovery Labs and various other 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;
- satisfactory completion of an FDA audit of clinical trial sites to assess compliance with GCP; and
- review and approval by the FDA of the NDA.

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 trial 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.

A drug being studied in clinical trials may be made available to individual patients in certain circumstances. Pursuant to the 21st Century Cures Act, or Cures Act, which was signed into law in December 2016, the manufacturer of an investigational drug for a serious disease or condition is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for individual patient access to such investigational drug. This requirement applies on the latter of 60 calendar days after the date of enactment of the Cures Act or the first initiation of a Phase 2 or Phase 3 trial of the investigational drug.

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. In addition to other benefits, such as the ability to 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.

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.

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 Amendments. The Hatch-Waxman Amendments 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, trial 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 of 2010, 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 $ 10,781 and $ 21,563 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 and by expanding the population potentially eligible for Medicaid drug benefits. 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. 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.
- 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").
- 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 annually report this information to CMS which makes it publicly available in a searchable format on a CMS website.
- 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 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.

Some of the provisions of the Affordable Care Act have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the Affordable Care Act. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the Affordable Care Act that are repealed. Thus, the full impact of the Affordable Care Act, any law replacing elements of it, or the political uncertainty surrounding its repeal or replacement on our business remains unclear. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

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:

- *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.
- *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.
- *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 pre-clinical 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 trial 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 pre-clinical 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

At December 31, 2016, 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 VI B.V. (the Netherlands, 100%);
- ProQR Therapeutics VII B.V. (the Netherlands, 100%);
- ProQR Therapeutics VIII B.V. (the Netherlands, 100%);
- ProQR Therapeutics IX B.V. (the Netherlands, 100%);
- ProQR Therapeutics I Inc. (United States, 100%).

D. Property, plants and equipment

We lease facilities of approximately 3,216 square meters in total, located at Zernikedreef in Leiden, the Netherlands, where our headquarters and our laboratories are located. 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 455 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 technologies we are building a pipeline of products that treat severe genetic disorders. Our lead product candidates are QR-010, a first-in-class RNA-based oligonucleotide designed to address the underlying cause of the disease by targeting the mRNA in CF patients that have the F508del mutation, QR-110, a first-in-class RNA-based oligonucleotide designed to address the underlying cause of Leber's congenital amaurosis Type 10 due to the p.Cys998X mutation in the CEP290 gene and QR-313, a first-in-class RNA-based oligonucleotide designed to address the underlying cause of dystrophic epidermolysis bullosa (DEB) due to mutations in exon 73 of the COL7A1 gene. Beyond that, we have launched a number of discovery programs including programs in Usher syndrome, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease, amyloid beta related disorders and Friedreich's ataxia.

To date, we have financed our operations primarily through our initial public offering, or IPO, our ATM facility 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, 2016, 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, € 4,598,000 in loans from a governmental body and approximately € 4,370,000 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, 2016, we had cash and cash equivalents of € 59,200,000. 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, 2016, 2015 and 2014, we incurred net losses of approximately € 39,103,000, € 20,832,000 and € 12,127,000, respectively. At December 31, 2016, we had an accumulated deficit of €75,733,000. 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 and QR-313 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, 2016 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 2017.

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 product candidate, QR-010, primarily consist of salaries, costs for production of the compound for clinical testing, and costs paid to CROs for our pre-clinical, toxicology 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, costs for production of the compound for clinical testing, and costs paid to CROs for our pre-clinical and toxicology 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 product candidate, QR-313 and our innovation unit, which is our internal discovery engine, which has been very active in building a pipeline 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, 2016, 2015 and 2014, we spent € 31,923,000, € 23,401,000 and € 10,267,000, 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 QR-313 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, QR-313 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, QR-313 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(d) 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 generated a limited amount of interest income. In 2016, as we held deposits in 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, 2016. 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, 2016, 2015 and 2014

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

	Year ended December 31,		
	2016	2015	2014
	(€ in thousands)		
Other income	1,828	3,235	313
Research and development costs	(31,923)	(23,401)	(10,267)
General and administrative costs	(9,478)	(6,837)	(6,507)
Operating result	**(39,573)**	**(27,003)**	**(16,461)**
Finance income and expense	470	6,171	4,334
Net loss (attributable to equity holders of the Company)	**(39,103)**	**(20,832)**	**(12,127)**
Other comprehensive income	(16)	1	—
Total comprehensive loss (attributable to equity holders of the Company)	**(39,119)**	**(20,831)**	**(12,127)**

Other income

For the periods ended December 31, 2016, 2015 and 2014, we had other income of € 1,828,000, € 3,235,000 and € 313,000, 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 € 31,923,000 for the year ended December 31, 2016 from € 23,401,000 for the year ended December 31, 2015 and € 10,267,000 for the year ended December 31, 2014. These costs were primarily related to our product candidates, QR-010, QR-110 and QR-313, 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 at a moderate level, although it fluctuates significantly from period to period.

The variances in research and development costs between the years ended December 31, 2016, 2015 and 2014 are mainly due to:

- costs we incurred on clinical trials for QR-010, particularly in 2015 and 2016;
- 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 40 at December 31, 2014 to 72 at December 31, 2015 and 100 at December 31, 2016;
- 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 GMP batches in preparation of our clinical studies;
- 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 € 9,478,000 for the year ended December 31, 2016 from € 6,837,000 for the year ended December 31, 2015 and € 6,507,000 for the year ended December 31, 2014. The increase was primarily related to:

- increased staff costs associated with the increase of our general and administrative staff from 19 full-time equivalent employees at December 31, 2014 to 27 full-time equivalent employees at December 31, 2015 and 33 full-time equivalent employees at December 31, 2016;
- 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 and 2016;
- 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. In 2016, these costs remained fairly stable; 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 remain fairly stable in upcoming years.

Finance income and expense

We had net finance income of € 470,000 for the year ended December 31, 2016, as compared to € 6,171,000 for the year ended December 31, 2015 and € 4,334,000 for the year ended December 31, 2014. The financial income 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, 2016, 2015 and 2014.

	Year ended December 31,		
	2016	2015	2014
	(€ in thousands)		
Net cash used in operating activities	(34,221)	(24,232)	(14,457)
Net cash used in investing activities	(2,539)	(1,324)	(1,233)
Net cash generated by financing activities	357	1,620	119,883
Net increase/(decrease) in cash and cash equivalents	**(36,403)**	**(23,936)**	**104,191**
Currency effect cash and cash equivalents	738	6,065	4,414
Cash and cash equivalents at the beginning of the period	94,865	112,736	4,129
Cash and cash equivalents at the end of the period	**59,200**	**94,865**	**112,736**

Net cash used in operating activities increased from € 14,457,000 in the year ended December 31, 2014 to € 24,232,000 in the year ended December 31, 2015 and € 34,221,000 in the year ended December 31, 2016. 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 € 1,233,000 in the year ended December 31, 2014 to € 1,324,000 in the year ended December 31, 2015 and € 2,539,000 in the year ended December 31, 2016. 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 decreased from € 119,883,000 in the year ended December 31, 2014 to € 1,620,000 in the year ended December 31, 2015 and to € 357,000 in the year ended December 31, 2016. 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 and 2016, cash generated by financing activities primarily included loans from a governmental body, totaling € 1,640,000 and € 370,000 respectively.

Cash and Funding Sources

The table below summarizes our main sources of financing for the years ended December 31, 2016, 2015 and 2014.

	Equity Capital	Convertible Loan	Government Borrowing	Total
	(€ in thousands)			
Year ended December 31, 2014	120,810	(2,500)	1,667	119,977
Year ended December 31, 2015	—	—	1,640	1,640
Year ended December 31, 2016	—	—	370	370
Total	120,810	(2,500)	3,677	121,987

Our source of financing in 2016 was funding from a governmental body amounting to € 370,000. Our source of financing in 2015 was funding from a governmental body amounting to € 1,640,000. 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.

In October 2015, we filed a shelf registration statement on Form S-3, which permitted: (a) the offering, issuance and sale by the Company of up to a maximum aggregate offering price of $ 200,000,000 of its ordinary shares, warrants and/or units; and (b) as part of the $ 200,000,000, the offering, issuance and sale by us of up to a maximum aggregate offering price of $ 60,000,000 of its ordinary shares that may be issued and sold under a sales agreement with Cantor Fitzgerald & Co in one or more at-the-market offerings. At December 31, 2016, no shares had been sold pursuant to its current at-the-market offering program.

At December 31, 2016, we had non-current liabilities of € 5,697,000, 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 through mid-2018. 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, 2016, 2015 and 2014:

	Year ended December 31,		
	2016	2015	2014
	(€ in thousands)		
Investments in tangible fixed assets	2,433	1,441	1,109
Investments in intangible assets	—	28	124
Total	**2,433**	**1,469**	**1,233**

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. Mid 2016, our two locations in the Netherlands were combined, facilitating further growth of our company and providing additional lab and office space. These changes led to increasing investments in tangible fixed assets in 2016, 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, 2016 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, 2016				
Borrowings	—	1,839	4,860	—
Trade payables and other payables	6,710	—	—	—
Total	**6,710**	**1,839**	**4,860**	**—**

Commitments

Rent

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

The lease expenditure charged to the income statement for operating leases in 2016 amounts to € 1,849,000 (2015: € 703,000, 2014: € 258,000). The total commitment as at December 31, 2016 amount to € 7,283,000 (2015: € 9,150,000, 2014: € 786,000).

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 F508del 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 we 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 € 8,856,000 at December 31, 2016 (2015: € 9,481,000). Of these obligations an amount of € 2,598,000 is due in 2017, 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

Other than as disclosed elsewhere in this annual report, we are not aware of any trends, uncertainties, demands, commitments or events for the period from January 1, 2016 to December 31, 2016 that are reasonably likely to have a material adverse effect on the Company’s net revenues, income, profitability, liquidity or capital resources, or that caused the reported financial information to be not necessarily indicative of future operating results or financial conditions. For a discussion of trends, see Item 5.A: “Operating results”.

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

This annual report contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. Refer to “Forward-looking statements” at the beginning of this report.

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 Zernikedreef 9, 2333 CK Leiden, the Netherlands.

Our supervisory board is currently composed of the following members, all of whom are independent under applicable NASDAQ standards and all of whom, with the exception of Mr. Antoine Papiernik are independent under the Dutch Corporate Governance Code (DCGC):

Name	Date of Birth	Position	Member Since	Term expires
Dinko Valerio	August 3, 1956	Member of the Supervisory Board (Chairman)	January 1, 2014	2020
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	2017
Henri Termeer	February 28, 1946	Member of the Supervisory Board	January 1, 2014	2020
James Shannon	June 5, 1956	Member of the Supervisory Board	June 21, 2016	2020
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.

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. In 2016 she joined the board of directors of CoLucid Pharmaceuticals. She also served on the board of directors of Cubist Pharmaceuticals for three years until its acquisition by Merck &Co., Inc. in 2015. She is member of the Corporate Advisory Board of 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. She earned her BSc in Pharmacology, with honors, from King's College London.

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, Gecko Biomedical and Rgenix. Mr. Papiernik has an MBA degree from the Wharton School of Business, University of Pennsylvania.

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 Boston Ballet, Museum of Science, WGBH and Project Hope. Mr. Termeer is also currently a board member of Abiomed Inc., Aveo Pharmaceuticals, 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.

James Shannon, MD has served on our Supervisory Board since June 2016. Mr. Shannon has had an extensive career in drug development and pharma. From 2012 until his retirement in 2015, Mr. Shannon was Chief Medical Officer at GlaxoSmithKline. Prior to that he was Global Head of Pharma Development at Novartis and Senior Vice-President, Clinical Development at Sterling Winthrop Pharmaceuticals. He held board positions at companies including Biotie, Circassia, Crucell, Endocyte, MannKind and Cerimon Pharmaceuticals. He received his undergraduate and postgraduate degrees at Queen's University of Belfast and is a Member of the Royal College of Physicians (UK). Mr. Shannon currently holds board positions at Mannkind Corp (USA), myTomonows (NL) and Immodulon (UK).

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.

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 Zernikedreef 9, 2333 CK 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	2018

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, 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 Zernikedreef 9, 2333 CK 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 June 21, 2016, 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 grant compensation to members of the supervisory board. The supervisory board will be reimbursed for their expenses.

Compensation of the Supervisory Board

The remuneration of the supervisory board members in 2016 is set out in the table below:

	2016			
	Short term employee benefits	Post-employment benefits	Share-based payment[1]	Total
Mr. Dinko Valerio	36	—	52	88
Mr. Henri Termeer	31	—	51	82
Mr. Antoine Papiernik	78	—	—	78
Ms. Alison Lawton	31	—	74	105
Mr. Paul Baart	82	—	—	82
Mr. James Shannon[2]	29	—	27	56
	287	—	204	491

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(d) to the financial statements included elsewhere in this annual report).

2 Mr. Shannon was appointed on June 21, 2016.

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 21, 2016, our shareholders approved an amendment of the compensation policy whereby members of the supervisory board may be granted an additional compensation in cash of $ 55,000 per year or a grant of options with an underlying value of $ 110,000 per year.

Compensation of the Management Board

The table below sets out a breakdown of the compensation in 2016 of each current member of the management board:

	2016			
	Short term employee benefits	Post-employment benefits	Share-based payment[1]	Total
	(€ in thousands)			
Mr. D.A. de Boer	429	7	391	827
Mr. R.K. Beukema	346	13	165	524
	775	**20**	**556**	**1,351**

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(d) 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 terms of four years. 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 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), James Shannon and Alison Lawton. Each member satisfies the independence requirements of the NASDAQ listing standards and Rule 10A-3(b)(1) under the Exchange Act and satisfies the criteria for independence set forth in best practice III.2.2 of the DCGC. Paul Baart 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 James Shannon (chairman), Dinko Valerio 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), Henri Termeer and Paul Baart. 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, 2016, we had a total of 133.3 employees (converted to FTE). Of these employees, 100.4 were engaged in research and development and 32.9 in general and administrative. For additional details we refer to note 17 to the financial statements. As far as we know, our employees are not represented by a labor union. We have never experienced any employment related work stoppages, and we consider our relations with our 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, 2016 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 23,346,856 ordinary shares outstanding as at December 31, 2016. 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, 2016, 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., Zernikedreef 9, 2333 CK, 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%
Jennison Associates LLC[2]	2,585,047	11.1%
Entities affiliated with Orbimed Advisors, LLC [3]	2,305,446	9.9%
Henri Termeer[4]	1,730,714	7.4%
Redmile Group, LLC [5]	1,578,174	6.8%
Appel B.V. [6]	1,171,208	5.0%
Supervisory Board Members and Management Board Members		
Henri Termeer[4]	1,756,789	7.5%
Dinko Valerio[7]	1,072,168	4.6%
Antoine Papiernik[8]	2,769,125	11.9%
Alison Lawton[9]	10,954	0.0%
Daniel de Boer[10]	1,243,587	5.3%
René Beukema[11]	413,137	1.8%
Paul Baart	—	0.0%
James Shannon	—	0.0%
All supervisory board members and management board members as a group (8 persons) [12]	**7,307,753**	**31.3%**

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 The registered office of Jennison Associates LLC is 466 Lexington Ave., New York, NY 10017. Based solely on the Schedule 13G/A filed by Jennison Associates LLC on February 3, 2017.

3 Consists of 973,446 ordinary shares held by OrbiMed Advisors, LLC and 1,332,000 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.

4 Consists of 1,730,714 ordinary shares and options to acquire 26,075 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016.

5 The registered office of Redmile Group, LLC is One Letterman Drive, Building D, Suite D3-300, San Francisco, CA 94129. Based solely on the Schedule 13G filed by Redmile Group, LLC on February 14, 2017.

6 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.

7 Consists of 588,457 ordinary shares and options to acquire 28,748 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016. 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.

8 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.

9 Consists of options to acquire 10,954 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016.

10 Consists of options to acquire 72,379 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016, and 1,171,208 ordinary shares held by Appel, B.V., which is owned and controlled by Daniel de Boer, our chief executive officer, as sole director.

11 Consists of 300,000 ordinary shares and options to acquire 113,137 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016.

12 Consists of 7,056,460 ordinary shares and options to acquire 251,293 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2016.

Holdings by U.S. Shareholders

As at December 31, 2016, approximately 89.5% of our outstanding shares were held by 2 record holders in the United States, which excludes shareholders whose shares were held in nominee or street name by brokers.

B. Related party transactions

Since January 1, 2016, 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, 2016, 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 year, quarter and the most recent six months:

	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
Year ended December 31, 2016	8.96	3.48
Quarterly highs and lows		
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
First quarter 2016	8.96	3.48
Second quarter 2016	6.76	3.55
Third quarter 2016	7.93	4.56
Fourth quarter 2016	8.70	3.95
Monthly highs and lows		
September 30, 2016	7.93	5.38
October 31, 2016	8.70	5.10
November 30, 2016	5.20	3.95
December 31, 2016	5.00	4.05
January 31, 2017	5.20	3.80
February 28, 2017	4.30	3.65

Since September 18, 2014, our ordinary shares have been listed on the NASDAQ Global Market under ticker symbol PRQR. On March 10, 2017, the closing price per share reported on the NASDAQ Global Market was $ 5.00.

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

General

We were incorporated on February 21, 2012 as a private company with limited liability ('*besloten vennootschap met beperkte aansprakelijkheid*') under Dutch law. In connection with our initial public offering in 2014, our shareholders resolved to amend our articles of association and to convert into a public company with limited liability by means of a Deed of Amendment and Conversion, pursuant to which, we converted to a public company with limited liability ('*naamloze vennootschap*') under the laws of the Netherlands. In connection with this conversion, our legal name changed from ProQR Therapeutics B.V. to ProQR Therapeutics N.V. Recently, on 22 June 2016 the articles of association were amended to (i) add certain places where general meeting of shareholders may be held and (ii) amend the term 'annual report' to 'report of the Management Board' to comply with the Implementation Act Annual Accounts Directive ('*Uitvoeringswet richtlijn jaarrekening*') (Bulletin of Acts and Decrees ('*Staatsblad*') 2015, 349), pursuant to which act this term has been amended accordingly.

Our company is registered with the Dutch Trade Register of the Chamber of Commerce ('*handelsregister van de Kamer van Koophandel en Fabrieken*') in Leiden, the Netherlands under number 54600790. Our corporate seat is in Leiden, the Netherlands, and our registered office is at Zernikedreef 9, 2333 CK Leiden, the Netherlands.

As of the date hereof, our authorized share capital is € 3,000,000, divided into 37,500,000 ordinary shares and 37,500,000 preferred shares, each with a nominal value of € 0.04. Under Dutch law, our authorized share capital is the maximum capital that we may issue without amending our articles of association.

Our ordinary shares are listed on the Nasdaq Global Market under the symbol "PRQR."

We have listed our ordinary shares in registered form and our shares are not certificated. We have appointed American Stock Transfer & Trust Company, LLC as our agent to maintain our shareholders register and to act as transfer agent, registrar and paying agent for the ordinary shares. Our ordinary shares are traded on the NASDAQ Global Market in book-entry form.

Articles of Association and Dutch Law

Set forth below is a summary of relevant information concerning the material provisions of our articles of association and applicable Dutch law. This summary does not constitute legal advice regarding those matters and should not be regarded as such.

Anti-Takeover Measure

To enable us to pursue our business strategy and the successful development of our product pipeline and to protect our interests and those of our stakeholders (including shareholders, employees and patient populations), our business strategy, our continuity and our independence against actual and potential threats, we have adopted an anti-takeover measure by granting a perpetual and repeatedly exercisable call option to a protection foundation, Stichting Continuity ProQR Therapeutics. The call option confers on the protection foundation the right to acquire under certain conditions 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 protection foundation's articles of association provide that it will act to promote and protect the best interests of us, our business and our stakeholders, including patient populations that may benefit from our products and pipeline, by opposing any influences that conflict with these interests and threaten to undermine our strategy, continuity, independence and identity. The board of the protection foundation is independent from us, our stakeholders and our subsidiaries.

Upon exercise of the call option, the preferred shares will be issued to the protection foundation for their nominal value, of which only 25% will be due upon issuance. The voting rights of our shares are based on nominal value and as we expect our shares to trade substantially in excess of nominal value, a foundation acquiring preferred shares issued at 25% of their nominal value can obtain significant voting power for a substantially reduced price and thus be used as a defensive measure. These preferred shares will have both a liquidation and dividend preference over our ordinary shares and will accrue cash dividends at a fixed rate with deficits in a preferred dividend being carried forward. The protection foundation may exercise the call option to acquire preferred shares in order to protect us from influences that do not serve our best interests and threaten to undermine our strategy, continuity, independence and identity. These influences may include a third-party acquiring a significant percentage of our ordinary shares, the announcement of a public offer for our ordinary shares, other concentration of control over our ordinary shares or any other form of pressure on us to alter our strategic policies.

Company's Shareholders' Register

All of our registered shares are registered in our shareholders' register. Subject to Dutch law and our articles of association, we must keep our shareholders' register accurate and up-to-date. Our shareholders' register shall be kept by our management board and, when it regards the subregister, on behalf of the management board by our agent. In our shareholders' register the names and addresses and other relevant details of all holders of registered shares are recorded, showing the date on which the shares were acquired, the date of the acknowledgement by or notification of us as well as the amount paid on each share. The shareholders' register also includes the names and addresses and other relevant details of those with a right usufruct ('*vruchtgebruik*') or a right of pledge ('*pandrecht*') in respect of such shares. The ordinary shares offered in this offering will be held through DTC, therefore DTC will be recorded in the shareholders register as the holder of those ordinary shares.

Shareholders, usufructuaries and pledgees whose particulars must be recorded in our shareholders' register are required to provide our management board with the necessary particulars in a timely fashion. Upon request, shareholders, usufructuaries and pledgees shall be provided with an extract of our shareholders' register in respect of their right to one or more registered shares.

Issuance of Shares and Pre-emptive Rights

Under Dutch law, shares are issued and rights to subscribe for shares are granted pursuant to a resolution of the general meeting of shareholders. Our articles of association provide that our general meeting of shareholders may only adopt such resolution upon a proposal of our management board, which proposal must have been approved by our supervisory board. Our general meeting of shareholders may authorize our management board to issue new shares or grant rights to subscribe for shares. The authorization can be granted and extended, in each case for a period not exceeding five years. For as long as such authorization is effective, our general meeting of shareholders will not have the power to issue shares and rights to subscribe for shares. Pursuant to our articles of association, our management board may only exercise the power to issue shares with the approval of our supervisory board.

On September 15, 2014, our general meeting of shareholders adopted a resolution pursuant to which our management board will be irrevocably authorized to, following approval of our supervisory board, issue up to 15% of our issued share capital for general purposes, plus 15% of our issued share capital for mergers, demergers, acquisitions and other strategic transactions and alliances, plus 15% of our issued share capital minus treasury shares for issuance under stock option plans, for a period of five years from the date of such resolution. Also, the call-option for preferred shares was issued to the protection foundation, as described above under "Anti-Takeover Measure".

Under Dutch law, in the event of an issuance of ordinary shares or granting of rights to subscribe for ordinary shares, each shareholder will have a pro rata preemptive right in proportion to the aggregate nominal value of the ordinary shares held by such holder. A holder of ordinary shares does not have a preemptive right with respect to the issuance of—or granting of rights to subscribe for (i) ordinary shares for consideration other than cash, or (ii) ordinary shares to our employees or employees of one of our group companies, or (iii) ordinary shares to persons exercising a previously granted right to subscribe for shares, or (iv) preferred shares.

The preemptive rights in respect of newly issued ordinary shares may be restricted or excluded by a resolution of the general meeting of shareholders. Our articles of association provide that our general meeting of shareholders may only adopt such resolution upon a proposal of our management board, which proposal must have been approved by our supervisory board. Our general meeting of shareholders may authorize our management board to restrict or exclude the preemptive rights in respect of newly issued ordinary shares. Such authorization for the management board can be granted and extended, in each case for a period not exceeding five years. For as long as such authorization is effective, our general meeting of shareholders will not have the power to limit or exclude preemptive rights and such authorization may not be revoked unless stipulated otherwise in the authorization. A resolution of the general meeting of shareholders to restrict or exclude the preemptive rights or to designate our management board as the authorized body to do so requires at least a two-thirds majority of the votes cast, if less than one half of our issued share capital is represented at the meeting.

Preferred shares do not carry preemptive rights in respect of newly issued ordinary shares or preferred shares, nor do holders of ordinary shares have preemptive rights in respect of newly issued preferred shares. The call option of the protection foundation to acquire newly issued preferred shares of the company, see “Description of Share Capital—Anti-Takeover Measure”, is an irrevocable and repeatedly exercisable right to subscribe for preferred shares.

On September 15, 2014, our general meeting of shareholders adopted a resolution pursuant to which our management board will be irrevocably authorized to —following approval of our supervisory board—limit or exclude the preemptive rights of holders of ordinary shares for a period of five years from the date of such resolution.

Repurchases of our Shares

Under Dutch law, we may not subscribe for newly issued shares in our own capital. We may acquire our shares, subject to applicable provisions and restrictions of Dutch law and our articles of association, to the extent that:

- such shares are fully paid-up;
- such shares are acquired for no consideration or such repurchase would not cause our shareholders’ equity to fall below an amount equal to the sum of the paid-up and called-up part of the issued share capital and the reserves we are required to maintain pursuant to Dutch law or our articles of association; and
- after the acquisition of shares, we and our subsidiaries would not hold, or would not hold as pledgees, shares having an aggregate nominal value that exceeds 50% of our issued share capital.

Other than shares acquired for no consideration or by universal succession, we may acquire shares only if our general meeting of shareholders has authorized the management board to do so. An authorization by the general meeting of shareholders for the acquisition of shares can be granted for a maximum period of 18 months. Such authorization must specify the number of shares that may be acquired, the manner in which these shares may be acquired and the price range within which the shares may be acquired. No authorization of the general meeting of shareholders is required if ordinary shares are acquired by us on NASDAQ with the intention of transferring such ordinary shares to our employees or employees of a group company pursuant to an arrangement applicable to them. Our articles of association further provide that a resolution of our management board to acquire fully paid-up shares in our share capital requires the approval of our supervisory board.

On September 15, 2014, our general meeting of shareholders adopted a resolution pursuant to which our management board will be authorized to acquire (i) up to 10 % of our issued share capital on NASDAQ or by other means for an 18-month period from the date of such resolution for a price per share not exceeding 110% of the market price of the ordinary shares on NASDAQ (with the market price deemed to be the average of the closing price on each of the five consecutive days of trading preceding the three trading days prior to the date of acquisition) and (ii) the ordinary shares issued under our Option Plan at a price not exceeding $1,000 per share.

Capital Reductions; Cancellation

At a general meeting of shareholders, our shareholders may resolve to reduce our issued share capital by (i) cancelling shares or (ii) reducing the nominal value of the shares by virtue of an amendment to our articles of association. In either case, this reduction would be subject to applicable statutory provisions. A resolution to cancel shares may only relate (x) to shares held by the company itself or in respect of which the company holds the depository receipts, and (y) to all preferred shares. Our articles of association provide that our general meeting of shareholders may only adopt such resolution upon a proposal of our management board, which proposal must have been approved by our supervisory board. In order to be adopted by the general meeting of shareholders, a resolution to reduce the capital requires a simple majority of the votes cast at a general meeting of shareholders if at least half the issued capital is represented at the meeting or at least two-thirds of the votes cast at the general meeting of shareholders if less than half of the issued capital is represented at the general meeting of shareholders.

A reduction of the nominal value of shares without repayment and without release from the obligation to pay up the shares must be effectuated proportionally on shares of the same class (unless all shareholders concerned agree to a disproportionate reduction). A resolution that would result in a reduction of capital requires approval of the meeting of each group of holders of shares of the same class whose rights are prejudiced by the reduction. In addition, a reduction of capital involves a two month waiting period during which creditors have the right to object to a reduction of capital under specified circumstances.

In the event that all preferred shares are cancelled, distributions shall be made to the protection foundation as sole holder of such preferred shares.

Corporate Objectives

Under our articles of association, our corporate objectives are:

- the development, bringing to market and exploitation of products and technologies in the field of biotechnology;
- the research and development of (or the commission to research and develop) patents, know-how and intellectual and industrial property;
- to make our products available to the patient populations that may benefit from such products and to maintain a suitable pipeline of products that may be beneficial for relevant patient populations;
- to participate in, to finance, to hold any other interest in and to conduct the management or supervision of other entities, companies, partnerships and businesses;
- to furnish guarantees, to provide security, to warrant performance in any other way and to assume liability, whether jointly and severally or otherwise, in respect of obligations of group companies or other parties; and
- to do anything which, in the widest sense of the words, is connected with or may be conducive to the attainment of these objects.

Amendment of Articles of Association

Our general meeting of shareholders, at the proposal of our management board, with the prior approval of our supervisory board, may resolve to amend our articles of association. A resolution taken by the general meeting of shareholders to amend our articles of association requires a simple majority of the votes cast.

General Meetings of Shareholders

General meetings of shareholders are held in Leiden, Amsterdam, Rotterdam, Schiphol Airport (municipality Haarlemmermeer), The Hague, Oegstgeest, Leidschendam, Katwijk, Noordwijk or in Wassenaar, the Netherlands. All shareholders and others entitled to attend general meetings of shareholders are authorized to attend the general meeting of shareholders, to address the meeting and, in so far as they have such right, to vote, either in person or by proxy.

We must hold at least one general meeting of shareholders each year, to be held within six months after the end of our financial year. A general meeting of shareholders shall also be held within three months after our management board has considered it to be likely that the company's equity has decreased to an amount equal to or lower than half of its paid up and called up capital. If the management board and supervisory board have failed to ensure that such general meetings of shareholders as referred to in the preceding sentences are held in a timely fashion, each shareholder and other person entitled to attend shareholders' meetings may be authorized by the Dutch court to convene the general meeting of shareholders.

Our management board and our supervisory board may convene additional extraordinary general meetings of shareholders whenever they so decide. Pursuant to Dutch law, one or more shareholders and/or others entitled to attend general meetings of shareholders, alone or jointly representing at least ten percent of our issued share capital may on their application, be authorized by the Dutch court to convene a general meeting of shareholders. The Dutch court will disallow the application if it does not appear to it that the applicants have previously requested that the management board or supervisory board convenes a shareholders' meeting and neither the management board nor the supervisory board has taken the necessary steps so that the shareholders' meeting could be held within eight weeks after the request.

General meetings of shareholders are convened by a notice which includes an agenda stating the items to be discussed. For the annual general meeting of shareholders the agenda will include, among other things, the adoption of our annual accounts, the appropriation of our profits or losses and proposals relating to the composition and filling of any vacancies of the management board or supervisory board. In addition, the agenda for a general meeting of shareholders includes such items as have been included therein by our management board or our supervisory board. Pursuant to Dutch law, one or more shareholders and/or others entitled to attend general meetings of shareholders, alone or jointly representing at least 3% of the issued share capital have the right to request the inclusion of additional items on the agenda of shareholders' meetings. Such requests must be made in writing, substantiated, or by a proposal for a resolution and received by us no later than the sixtieth day before the day the relevant general meeting of shareholders is held. No resolutions will be adopted on items other than those which have been included in the agenda.

We will give notice of each general meeting of shareholders by publication on our website and, to the extent required by applicable law, in a Dutch daily newspaper with national distribution, and in any other manner that we may be required to follow in order to comply with Dutch law, applicable stock exchange and SEC requirements. We will observe the statutory minimum convening notice period for a general meeting of shareholders.

Pursuant to our articles of association, our management board may determine a record date ('*registratiedatum*') of 28 calendar days prior to a general meeting of shareholders to establish which shareholders and others with meeting rights are entitled to attend and, if applicable, vote in the general meeting of shareholders. The record date, if any, and the manner in which shareholders can register and exercise their rights will be set out in the convocation notice of the general meeting of shareholders. Our articles of association provide that a shareholder must notify the company in writing of his identity and his intention to attend (or be represented at) the general meeting of shareholders, such notice to be received by us ultimately on the seventh day prior to the general meeting of shareholders. If this requirement is not complied with or if upon direction of the company to that effect no proper identification is provided by any person wishing to enter the general meeting of shareholders, the chairman of the general meeting of shareholders may, in his sole discretion, refuse entry to the shareholder or his proxy holder.

Pursuant to our articles of association, our general meeting of shareholders is chaired by the chairman of our supervisory board. If the chairman of our supervisory board is absent and has not charged another person to chair the meeting in his place, the supervisory board members present at the meeting shall appoint one of them to be chairman. If no supervisory board members are present at the general meeting of shareholders, the general meeting of shareholders will be chaired by our CEO or, if our CEO is absent, another management board member present at the meeting and, if none of them is present, the general meeting of shareholders shall appoint its own chairman. The person who should chair the meeting may appoint another person in his stead.

The chairman of the general meeting of shareholders may decide at his discretion to admit other persons to the meeting. The chairman of the general meeting of shareholders shall appoint another person present at the shareholders' meeting to act as secretary and to minute the proceedings at the meeting. The chairman of the general meeting of shareholders may instruct a civil law notary to draw up a notarial report of the proceedings at the company's expense, in which case no minutes need to be taken. The chairman of the general meeting of shareholders is authorized to eject any person from the general meeting of shareholders if the chairman considers that person to disrupt the orderly proceedings. The general meeting of shareholders shall be conducted in the English language.

Voting Rights and Quorum Requirements

In accordance with Dutch law and our articles of association, each issued ordinary share and preferred share confers the right on the holder thereof to cast one vote at the general meeting of shareholders. The voting rights attached to any shares held by us or our direct or indirect subsidiaries are suspended as long as they are held in treasury. Dutch law does not permit cumulative voting for the election of management board members or supervisory board members.

Voting rights may be exercised by shareholders or by a duly appointed proxy holder (the written proxy being acceptable to the chairman of the general meeting of shareholders) of a shareholder, which proxy holder need not be a shareholder. Our articles of association do not limit the number of shares that may be voted by a single shareholder.

Under our articles of association, blank votes, abstentions and invalid votes shall not be counted as votes cast. Further, shares in respect of which a blank or invalid vote has been cast and shares in respect of which the person with meeting rights who is present or represented at the meeting has abstained from voting are counted when determining the part of the issued share capital that is present or represented at a general meeting of shareholders. The chairman of the general meeting of shareholders shall determine the manner of voting and whether voting may take place by acclamation.

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. To this extent, our practice varies from the requirement of NASDAQ Listing Rule 5620(c), which requires an issuer to provide in its bylaws for a generally applicable quorum, and that such quorum may not be less than one-third of the outstanding voting shares.

Resolutions of the general meeting of shareholders are adopted by a simple majority of votes cast without quorum requirement, except where Dutch law or our articles of association provide for a special majority and/or quorum in relation to specified resolutions.

The chairman of the general meeting of shareholders shall decide on the method of voting and may determine the voting procedure. The determination made by the chairman of the general meeting of shareholders with regard to the results of a vote shall be decisive. However, where the accuracy of the chairman's determination is contested immediately after it has been made, a new vote shall take place if the majority of the general meeting of shareholders so requires or, where the original vote did not take place by response to a roll call or in writing, if any party with voting rights present at the meeting so requires.

Our management board will keep a record of the resolutions passed at each general meeting of shareholders. The record shall be available at our office for inspection by any person entitled to attend general meetings of shareholders and upon request a copy of or extract from the record will be provided to such person at no more than the cost price.

Our articles of association and Dutch law provide that resolutions of our management board concerning a material change in the identity or character of the company or our business are subject to the approval of the general meeting of shareholders. Such changes include in any event:

- a transfer of all or materially all of our business to a third party;
- the entry into or termination of a long-lasting alliance of the company or of a subsidiary either with another entity or company, or as a fully liable partner of a limited partnership or partnership, if this alliance or termination is of significant importance for the company; and
- the acquisition or disposition of an interest in the capital of a company by the company or by a subsidiary with a value of at least one third of the value of the assets, according to the balance sheet with explanatory notes or, if the company prepares a consolidated balance sheet, according to the consolidated balance sheet with explanatory notes in the company's most recently adopted annual accounts.

Adoption of Annual Accounts and Discharge of Management and Supervisory Liability

Pursuant to Dutch law, we are required to publish our annual accounts within eight days after adoption and ultimately within 13 months after the end of our financial year.

Each year within five months after the end of our financial year, save where this period is extended for a maximum of six months by the general meeting of shareholders on account of special circumstances, our management board will prepare the annual accounts. The annual accounts must be accompanied by an auditor's certificate, a report of the management board and certain other mandatory information and must be made available for inspection by our shareholders at our offices within the same period. Under Dutch law, the general meeting of shareholders may appoint and remove our independent auditors, as referred to in Section 2:393 Dutch Civil Code, who audit the annual accounts. If the general meeting of shareholders fails to appoint an independent auditor, the auditor will be appointed by the supervisory board or, if the supervisory board fails to do so, the management board. The annual accounts are adopted by our shareholders at the general meeting of shareholders and will be prepared in accordance with Part 9 of Book 2 of the Dutch Civil Code.

The adoption of the annual accounts by our shareholders does not release our management board members and our supervisory board members from liability for acts reflected in those documents. Any such release from liability requires a separate shareholders' resolution.

Our financial reporting will be subject to the supervision of the Dutch regulator AFM. The AFM will review the content of the financial reports and has the authority to approach us with requests for information if, on the basis of publicly available information, it has reasonable doubts as to the integrity of our financial reporting. For a more detailed description we refer to the description below under the heading "—Dutch Financial Reporting Supervision Act."

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, of which none will be outstanding on completion of this offering. 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 do not anticipate paying any dividends for the foreseeable future.

Liquidation and Dissolution

The general meeting of shareholders may, based on a proposal by our management board, which proposal has been approved by our supervisory board, resolve to dissolve the company by a resolution passed by a simple majority of the votes cast. In the event of the company being dissolved, the liquidation shall be effected by our management board under the supervision of the supervisory board, unless the general meeting of shareholders decides otherwise.

In the event of a dissolution and liquidation, the assets remaining after payment of all of the company's debts (including any liquidation expenses) are to be distributed (i) firstly to the holders, if any, of preferred shares the nominal value of the preferred shares (to the extent paid-up) plus unpaid accrued dividends and deficits (if any) in preferred dividends, (ii) the balance remaining to the holders of ordinary shares in proportion to the aggregate nominal value of their ordinary shares. The liquidation and all distributions referred to in this paragraph will be made in accordance with the relevant provisions of Dutch law.

Limitations on Non-Residents and Exchange Controls

There are no limits under the laws of the Netherlands or in our articles of association on non-residents of the Netherlands holding or voting our ordinary shares. Under Dutch law, there currently are no exchange controls applicable to the transfer of dividends or other distributions with respect to, or of the proceeds from the sale of, shares in a Dutch company, to persons outside the Netherlands.

Netherlands Squeeze-Out Proceedings

Pursuant to Section 2:92a of the Dutch Civil Code, a shareholder who for its own account (or together with its group companies) provides at least 95% of our issued share capital may institute proceedings against our other shareholders jointly for the transfer of their shares to it. The proceedings are held before the Enterprise Chamber of the Amsterdam Court of Appeal ('*Ondernemingskamer*') and can be instituted by means of a writ of summons served upon each of the minority shareholders in accordance with the provisions of the Dutch Code of Civil Procedure ('*Wetboek van Burgerlijke Rechtsvordering*'). The Enterprise Chamber may grant the claim for squeeze-out in relation to all minority shareholders and will determine the price to be paid for the shares, if necessary after appointment of one or three experts who will offer an opinion to the Enterprise Chamber on the value of the shares of the minority shareholders. Once the order to transfer by the Enterprise Chamber of the Amsterdam Court of Appeal becomes final and irrevocable, the majority shareholder that instituted the squeeze-out proceedings shall give written notice of the date and place of payment and the price to the holders of the shares to be acquired whose addresses are known to the majority shareholder. Unless the addresses of all minority shareholders are known to the majority shareholder acquiring the shares, the majority shareholder is required to publish the same in a newspaper with a national circulation.

A shareholder that provides a majority of our issued share capital, but less than the 95% required to institute the squeeze-out proceedings described above, may seek to propose and implement one or more restructuring transactions with the objective to obtain at least 95% of our issued share capital and thus to be allowed to initiate squeeze-out proceedings. Those restructuring transactions could, amongst other things, include a legal merger or demerger involving our company, a contribution of cash and/or assets against issuance of shares involving our company, the issue of new shares to the majority shareholder while excluding any pre-emption rights of minority shareholders in relation to such issuance or an asset sale transaction.

In Dutch public takeover practice, depending on the circumstances, an asset sale transaction is sometimes used as a way to squeeze out minority shareholders, for example, after a successful public offer, or tender offer, through which the offeror acquires a supermajority, but less than all, of the shares. In such a scenario, the business of the target company would be sold to an offeror, a buyer or a special purpose vehicle, followed by the liquidation of the target company. The purchase price would be distributed to all shareholders in proportion to their respective shareholding as liquidation proceeds, thus separating the business from the company in which minority shareholders participated.

Under our articles of association, any proposal to sell and transfer all of our assets and to dissolve and liquidate our company is subject to approval by a majority of the votes cast in our general meeting of shareholders which must be preceded by a proposal by our management board, which must be approved by our supervisory board.

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) or statutory directors (‘*bestuurders*’) or supervisory directors (‘*commissarissen*’) of a company resident in the Netherlands; 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.

Dividend 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[1] 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.

1 Qualifying foreign subsidiaries are entities established in Aruba, Curacao, St. Maarten, the BES islands or in a state which has concluded a double tax treaty with the Netherlands.

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%, but only insofar the holder's net investments assets exceed the tax-free capital threshold of EUR 24,437 (or EUR 48,874 in case of a fiscal partnership). 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. 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 or has a deemed enterprise for activities performed as statutory director ('*bestuurder*') or supervisory director ('*commissaris*') of a company resident of the Netherlands; 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.

Residence

A shareholder will not become resident or deemed resident in the Netherlands for tax purposes by reason only of holding 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;
- 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 tested, would be measured by the 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.

Based on the average value of our gross assets, we believe that we may be classified as a PFIC for the 2016 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 are 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 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, 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 (and with respect to any of our subsidiaries that also may be determined to be PFICs), 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 currently do not engage in hedging transactions to protect against uncertainty in future exchange rates between particular foreign currencies and the euro. 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, 2016 there was a net liability in U.S. Dollars of € 2.4 million (2015: € 1.1 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, 2016, we had one loan with a fixed interest, amounting to € 5,697,000 (2015: € 4,824,000).

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 banks which meet our defined minimum credit ratings.

Liquidity Risk

Management forecasts our liquidity requirements to ensure that there is sufficient cash to meet operational needs. We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements through mid-2018. 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 than 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 € 66.9 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, 2016). 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, 2016.

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, 2016. Based on this assessment, management concluded that the Company's internal control over financial reporting was effective as at December 31, 2016.

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, 2016, 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 qualifies as an "audit committee financial expert," as defined by the SEC and as determined by our supervisory board. In addition, he satisfies the independence requirements of the NASDAQ listing standards and Rule 10A-3(b)(1) under the Exchange Act and 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 2016, 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 effective as of June 22, 2016.
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)
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)

Exhibit No.	Description
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)
4.12*††	Amendment Number 4 to Exclusive Patent License Agreement, dated as of September 28, 2016, by and between the Registrant and The General Hospital Corporation d/b/a Massachusetts General Hospital
4.13*†††	Lease Agreement for the Registrant's facility in Zernikedreef in Leiden, the Netherlands
4.14*††	License Agreement between Radboudumc as Licensor, and ProQR Therapeutics N.V. as Licensee dated as of April 17, 2014
8.1*	Subsidiaries of the Registrant
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.

†† Application has been made for confidential treatment as to certain portions of this exhibit, which portions have been omitted and filed separately with the Securities and Exchange Commission.

††† English summary of original Dutch document.

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, 2017

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

INDEX TO FINANCIAL STATEMENTS

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, 2016 and 2015, 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, 2016 (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, 2016 and 2015, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2016, 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, 2017

PROQR THERAPEUTICS N.V.

Consolidated Statement of Financial Position

		December 31, 2016	December 31, 2015
		(€ in thousands)	
Assets			
Intangible assets	*7*	90	141
Property, plant and equipment	*8*	3,438	2,199
Non-current assets		**3,528**	**2,340**
Social security and other taxes	*9*	395	956
Prepayments and other receivables	*10*	2,420	1,948
Cash and cash equivalents	*11*	59,200	94,865
Current assets		**62,015**	**97,769**
Total assets		**65,543**	**100,109**
Shareholders' equity			
Share capital		934	934
Share premium reserve		123,597	123,595
Equity settled employee benefits reserve		4,353	1,899
Translation reserve		(15)	1
Accumulated deficit		(75,733)	(36,630)
Total equity	*12*	**53,136**	**89,799**
Liabilities			
Borrowings		5,697	4,824
Finance lease liabilities		—	—
Non-current liabilities	*13*	**5,697**	**4,824**
Finance lease liabilities		—	15
Trade payables		328	885
Social security and other taxes		312	235
Pension premiums		13	16
Deferred income		—	144
Other current liabilities		6,057	4,191
Current liabilities	*14*	**6,710**	**5,486**
Total liabilities		**12,407**	**10,310**
Total equity and liabilities		**65,543**	**100,109**

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,		
		2016	2015	2014
		(€ in thousands)		
Other income	*15*	1,828	3,235	313
Research and development costs	*16*	(31,923)	(23,401)	(10,267)
General and administrative costs		(9,478)	(6,837)	(6,507)
Total operating costs		(41,401)	(30,238)	(16,774)
Operating result		**(39,573)**	**(27,003)**	**(16,461)**
Financial income and expense	*18*	470	6,171	4,334
Result before corporate income taxes		**(39,103)**	**(20,832)**	**(12,127)**
Income taxes	*19*	—	—	—
Net loss (attributable to equity holders of the Company)		**(39,103)**	**(20,832)**	**(12,127)**
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		(16)	1	—
Total comprehensive loss (attributable to equity holders of the Company)		**(39,119)**	**(20,831)**	**(12,127)**
Share information	*20*			
Weighted average number of shares outstanding		23,346,507	23,343,262	11,082,801
Earnings per share for result attributable to the equity holders of the Company (expressed in Euro per share)				
Basic and diluted loss per share		€ (1.68)	€ (0.89)	€ (1.09)

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	Share Premium Reserve	Equity Settled Employee Benefit Reserve	Translation Reserve	Accumulated Deficit	Total Equity
	(€ in thousands)	(€ in thousands)	(€ in thousands)	(€ in thousands)	(€ in thousands)	(€ in thousands)
Balance at January 1, 2014	**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**
Net loss	—	—	—	—	(39,103)	(39,103)
Other comprehensive income	—	—	—	(16)	—	(16)
Recognition of share-based payments	—	—	2,454	—	—	2,454
Shares options exercised	0	2	—	—	—	2
Balance at December 31, 2016	**934**	**123,597**	**4,353**	**(15)**	**(75,733)**	**53,136**

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

PROQR THERAPEUTICS N.V.

Consolidated Statement of Cash Flows

	Year Ended December 31,		
	2016	2015	2014
	(€ in thousands)		
Cash flow from operating activities			
Net loss	(39,119)	(20,831)	(12,127)
Adjustments for:			
Depreciation	1,245	480	126
Share-based payment expenses	2,454	1,212	646
Financial income and expense	(470)	(6,171)	(4,334)
Changes in working capital	1,433	637	1,090
Corporate income tax paid	—	—	—
Interest received	236	441	142
Net cash used in operating activities	**(34,221)**	**(24,232)**	**(14,457)**
Cash flow from investing activities			
Purchases of intangible assets	—	(28)	(124)
Purchases of property, plant and equipment	(2,539)	(1,296)	(1,109)
Net cash used in investing activities	**(2,539)**	**(1,324)**	**(1,233)**
Cash flow from financing activities			
Net proceeds from issuance of shares	—	—	118,250
Proceeds from exercise of share options	2	14	—
Proceeds from borrowings	370	1,640	1,667
Redemption of financial lease	(15)	(34)	(34)
Net cash generated by financing activities	**357**	**1,620**	**119,883**
Net increase/(decrease) in cash and cash equivalents	**(36,403)**	**(23,936)**	**104,193**
Currency effect cash and cash equivalents	738	6,065	4,414
Cash and cash equivalents at the beginning of the year	94,865	112,736	4,129
Cash and cash equivalents at the end of the year	**59,200**	**94,865**	**112,736**

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 Zernikedreef 9, 2333 CK Leiden, the Netherlands.

At December 31, 2016, 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 VI B.V. (the Netherlands, 100%);
- ProQR Therapeutics VII B.V. (the Netherlands, 100%);
- ProQR Therapeutics VIII B.V. (the Netherlands, 100%);
- ProQR Therapeutics IX 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 2016 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.

(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(d) 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, 2016, 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 as 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 of disposal 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 2017, 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 2018, 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, 2016 there was a net liability in U.S. Dollars of € 2.4 million (2015: € 1.1 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, 2016 would have affected the measurement of our cash balances denominated in a U.S. Dollar and affected equity and profit or loss by € 2.5 million (2015: € 5.2 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 with a fixed interest, amounting to € 5,697,000 at December 31, 2016 (2015: € 4,824,000). 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, Rabobank and Wells Fargo. 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).

At December 31, 2016 and December 31, 2015, substantially all of our cash and cash equivalents were placed at two large institutions, Rabobank and ABN Amro. In 2016, this also included Wells Fargo. All institutions are highly rated (ratings of Aa2, A1 and A2 for Rabobank, ABN Amro and Wells Fargo 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, 2016				
Borrowings	—	1,839	4,860	—
Trade payables and other payables	6,710	—	—	—
Total	**6,710**	**1,839**	**4,860**	**—**
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**	**—**

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, 2016 and 2015.

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 comprises 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, 2015			
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**
Additions	—	—	—
Amortization	—	(51)	(51)
Movement for the period	**—**	**(51)**	**(51)**
Balance at December 31, 2016			
Cost	39	152	191
Accumulated amortization	—	(101)	(101)
Carrying amount	**39**	**51**	**90**

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 for 2016 is included in the general and administrative costs for an amount of € 51,000 (2015: € 50,000).

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, 2015				
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**
Additions	1,166	806	461	2,433
Depreciation	(499)	(340)	(332)	(1,171)
Transfer	(196)	—	196	—
Disposals	(23)	—	—	(23)
Movement for the period	**448**	**466**	**325**	**1,239**
Balance at December 31, 2016				
Cost	1,847	1,957	1,283	5,087
Accumulated depreciation	(508)	(660)	(481)	(1,649)
Carrying amount	**1,339**	**1,297**	**802**	**3,438**

The depreciation charge for 2016 is included in the research and development costs for an amount of € 907,000 (2015: € 361,000) and in the general and administrative costs for an amount of € 264,000 (2015: € 62,000).

9. Social Security and Other Taxes

	December 31, 2016	December 31, 2015
	(€ in thousands)	
Value added tax	395	953
Wage tax	—	3
	395	956

All receivables are considered short-term and due within one year.

10. Prepayments and Other Receivables

	December 31, 2016	December 31, 2015
	(€ in thousands)	
Prepayments	1,250	1,401
Other receivables	1,170	547
	2,420	1,948

All receivables are considered short-term and due within one year.

11. Cash and Cash Equivalents

	December 31, 2016	December 31, 2015
	(€ in thousands)	
Cash at banks	56,354	94,865
Bank deposits	2,846	—
	59,200	94,865

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 2016		Number of shares 2015		Number of shares 2014	
	Ordinary	Preferred	Ordinary	Preferred	Ordinary	Preferred
In issue at January 1	23,345,965	—	23,338,154	—	6,108,152	—
Issued for cash	—	—	—	—	9,490,336	8,265,179
Conversion of preferred shares	—	—	—	—	8,265,179	(8,265,179)
Exercise of share options	891	—	7,811	—	—	—
Treasury shares issued	—	—	—	—	(525,513)	—
In issue at December 31 – fully paid	**23,346,856**	**—**	**23,345,965**	**—**	**23,338,154**	**—**

The authorized share capital of the Company amounting to € 3,000,000 consists of 37,500,000 ordinary shares and 37,500,000 preference shares with a par value of € 0.04 per share. At December 31, 2016, 24,520,814 ordinary shares were issued and fully paid in cash, of which 1,173,958 were held by the Company as treasury shares (2015: 1,174,849).

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 against 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.

On October 2, 2015, the Company filed a shelf registration statement, which permitted: (a) the offering, issuance and sale by the Company of up to a maximum aggregate offering price of $ 200,000,000 of its ordinary shares, warrants and/or units; and (b) as part of the $ 200,000,000, the offering, issuance and sale by us of up to a maximum aggregate offering price of $ 60,000,000 of its ordinary shares that may be issued and sold under a sales agreement with Cantor Fitzgerald & Co in one or more at-the-market offerings. At December 31, 2016, no shares had been sold pursuant to its current at-the-market offering program.

(b) 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'.

(c) Translation reserve

The translation reserve comprises all foreign currency differences arising from the translation of the financial statements of foreign operations.

(d) 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 € 2,454,000 in 2016 (2015: € 1,212,000, 2014: € 646,000), of which € 1,480,000 (2015: € 801,000, 2014: € 404,000) was recorded in general and administrative costs and € 974,000 (2015: € 411,000, 2014: € 242,000) 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 2016	Options granted in 2015	Options granted in 2014
Risk-free interest rate	1.467%	1.497%	0.616%
Expected dividend yield	0%	0%	0%
Expected volatility	86.3%	86.8%	88.6%
Expected life in years	5 years	5 years	5 years

The resulting weighted average grant date fair value of the options amounted to € 3.72 in 2016 (2015: € 10.35, 2014: € 2.58). 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:

	2016		2015		2014	
	Number of options	Average exercise price	Number of options	Average exercise price	Number of options	Average exercise price
Balance at January 1	1,108,935	€ 4.19	998,765	€ 2.78	379,323	€ 1.11
Granted	1,214,126	€ 5.49	125,798	€ 15.27	691,722	€ 3.52
Forfeited	(116,181)	€ 4.64	(7,817)	€ 4.64	(11,095)	€ 1.20
Exercised	(891)	€ 2.38	(7,811)	€ 1.78	(61,185)	€ 1.11
Lapsed	—	—	—	—	—	—
Balance at December 31	**2,205,989**	**€ 4.88**	**1,108,935**	**€ 4.19**	**998,765**	**€ 2.78**
Exercisable at December 31	615,246		339,352		94,729	

The options outstanding at December 31, 2016 had an exercise price in the range of € 1.11 to € 20.34 (2015: € 1.11 to € 20.34, 2014: € 1.11 to € 12.15) and a weighted-average contractual life of 8.3 years (2015: 8.3 years, 2014: 9.2 years).

The weighted-average share price at the date of exercise for share options exercised in 2016 was € 4.23 (2015: € 19.30, 2014: € 3.04).

Please refer to Note 23 for the options granted to key management personnel.

13. Non-current liabilities

(a) Borrowings

	December 31, 2016	December 31, 2015
	(€ in thousands)	
Innovation credit	4,598	4,228
Accrued interest on innovation credit	1,099	596
	5,697	4,824

Innovation credit ("Innovatiekrediet")

On June 1, 2012, ProQR was awarded an Innovation credit by the Dutch government, through its agency RVO of the Ministry of Economic Affairs, for the Company's cystic fibrosis program. Amounts were drawn under this facility in the course of the years 2013 through 2016. The credit covers 35% of the costs incurred in respect of the program up to an initial maximum of € 5.0 million.

The credit is interest-bearing at a rate of 10% per annum. The credit, including accrued interest, is repayable in three installments on November 30, 2018, November 30, 2019 and November 30, 2020, 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

	2016	2015
	(€ in thousands)	
Balance at January 1	15	49
Initial recognition new finance leases	—	—
Interest expense accrued	—	—
Payment of finance lease liabilities	(15)	(34)
Balance at December 31	**—**	**15**
Current portion at December 31	—	(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 nil in 2016 (2015: € 48,000).

Future minimum lease payments under finance leases as at December 31, 2016 are as follows:

	2016		2015	
	Minimum payments	Present value of payments	Minimum payments	Present value of payments
	(€ in thousands)			
Less than 1 year	—	—	15	15
Between 1 and 5 years	—	—	—	—
More than 5 years	—	—	—	—

The interest used for the present value of payments is 2%.

14. Current Liabilities

	December 31, 2016	December 31, 2015
	(€ in thousands)	
Current portion finance lease liabilities	—	15
Trade payables	328	885
Social securities and other taxes	312	235
Pension premiums	13	16
Deferred income	—	144
Accrued expenses and other liabilities	6,057	4,191
	6,710	**5,486**

At December 31, 2015, current liabilities included 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.

15. Other income

	2016	2015	2014
	(€ in thousands)		
Grant income	1,632	3,188	313
Rental income from property subleases	196	47	—
	1,828	**3,235**	**313**

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 through 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 € 31,923,000 in 2016 (2015: € 23,401,000, 2014: € 10,267,000) 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

	2016	2015	2014
	(€ in thousands)		
Wages and salaries	10,184	7,128	3,845
Social security costs	1,093	596	320
Pension costs — defined contribution plans	764	478	217
Equity-settled share based payments	2,454	1,212	646
	14,495	**9,414**	**5,028**
Average number of employees for the period	133.4	86.1	37.8

Employees per activity at December 31 (converted to FTE):

	December 31, 2016	December 31, 2015	December 31, 2014
Research and Development	100.4	72.4	40.1
General and Administrative	32.9	27.1	18.7
Total number of employees at December 31 (converted to FTE)	**133.3**	**99.5**	**58.8**

Of all employees 128.3 FTE are employed in the Netherlands (2015: 94.5 FTE).

Included in the wages and salaries for 2016 is a credit of € 807,000 (2015: € 372,000, 2014: € 301,000) with respect to WBSO subsidies.

18. Financial Income and Expense

	2016	2015	2014
	(€ in thousands)		
Interest income:			
Current accounts and deposits	270	501	183
Interest costs:			
Interest on loans and borrowings	(538)	(395)	(265)
Foreign exchange result:			
Net foreign exchange benefit/(loss)	738	6,065	4,416
	470	**6,171**	**4,334**

19. Income Taxes

The calculation of the tax charge is as follows:

	2016	2015	2014
	(€ in thousands)		
Income tax based on domestic rate (25%)	9,776	5,208	3,032
Tax effect of:			
Non-deductible expenses	(622)	(309)	(207)
Tax incentives	(46)	136	2,065
Current year losses for which no deferred tax asset was recognized	(9,045)	(5,035)	(4,890)
Change in unrecognized deductible temporary differences	(63)	—	—
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, 2016, the Company has a total amount of € 82.9 million (2015: € 46.9 million, 2014: € 26.8 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.

	2016	2015	2014
Result attributable to equity holders of the Company (€ in thousands)	(39,103)	(20,832)	(12,127)
Weighted average number of shares	23,346,507	23,343,262	11,082,801
Basic (and diluted) earnings per share (€ per share)	**€ (1.68)**	**€ (0.89)**	**€ (1.09)**

(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, the Netherlands where it currently has concluded rental agreements for laboratory space and offices. In addition, the Company has one office in the US.

The lease expenditure charged to the income statement in 2016 amounts to € 1,849,000 (2015: € 703,000, 2014: € 258,000). The future aggregate minimum lease payments under non-cancellable operating leases are as follows:

	December 31, 2016	December 31, 2015	December 31, 2014
		(€ in thousands)	
Less than 1 year	1,775	1,938	509
Between 1 and 5 years	5,508	7,212	277
More than 5 years	—	—	—
Total	**7,283**	**9,150**	**786**

The Company leases out a part of its office in the U.S. In 2016, total sublease income amounted to € 196,000 (2015: € 47,000, 2014: nil), which is recorded in other income. At 31 December, the future minimum lease payments under non-cancellable leases are receivable as follows:

	December 31, 2016	December 31, 2015	December 31, 2014
		(€ in thousands)	
Less than 1 year	463	185	—
Between 1 and 5 years	—	—	—
More than 5 years	—	—	—
Total	**463**	**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 has entered into various other Patent License Agreements, including those with Radboud University Medical Center, Leiden University Medical Centre and PARI Pharma GmbH, under which the Company is granted world-wide exclusive licenses pursuant to which the Company may have certain royalty obligations in relation to its product candidates. Pursuant to the terms of these agreements, the Company has made upfront payments, is obligated to make milestone payments and has to make sales-based royalty payments after market authorization. In specific cases, the Company has the option to make a one-time payment to buy of royalty obligations or in case the Company terminates an agreement before or after regulatory approval of the product. The Company may terminate an agreement for any reason.

(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 € 8,856,000 at December 31, 2016 (2015: € 9,481,000). Of these obligations an amount of € 6,258,000 is due in 2017, 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 21, 2016, Mr. James Shannon was appointed to our supervisory board. The remuneration of the supervisory board members in 2016 is set out in the table below:

	2016			
	Short term employee benefits	Post-employment benefits	Share-based payment	Total
Mr. Dinko Valerio	36	—	52	88
Mr. Henri Termeer	31	—	51	82
Mr. Antoine Papiernik	78	—	—	78
Ms. Alison Lawton	31	—	74	105
Mr. Paul Baart	82	—	—	82
Mr. James Shannon	29	—	27	56
	287	**—**	**204**	**491**

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 2014 remuneration 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**

As at December 31, 2016:

- Mr. Valerio holds 1,043,420 ordinary shares in the Company, as well as 56,261 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. In 2016, Mr. Valerio was granted 23,989 options at an average exercise price of € 6.08 per option.
- Mr. Termeer holds 1,730,714 ordinary shares in the Company as well as 52,698 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. In 2016, Mr. Termeer was granted 23,989 options at an average exercise price of € 6.08 per option.

- 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 36,809 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. In 2016, she was granted 23,989 options with an average exercise price of € 6.08 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.
- Mr. James Shannon holds 33,069 options. In 2016, he was granted 33,069 options at an exercise price of € 4.32 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.

(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 2016 amounted to € 3,038,000 with the details set out in the table below:

	2016			
	Short term employee benefits	Post employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. D.A. de Boer	429	7	391	827
Mr. R.K. Beukema	346	13	165	524
Management Board	775	20	556	1,351
Senior Management	1,020	48	619	1,687
	1,795	**68**	**1,175**	**3,038**

1 Short term employee benefits 2016 includes a bonus for Mr. Daniel de Boer, of € 131,000 based on goals realised in 2016.
2 Short term employee benefits 2016 includes a bonus for Mr. René Beukema, of € 76,000 based on goals realised in 2016.

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 includes a bonus for Mr. Daniel de Boer of € 100,000 based on goals realised in 2015.
2 Short term employee benefits includes a bonus for Mr. René Beukema of € 46,000 based on goals realised in 2015.

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[1]	696	10	195	901
Mr. R.K. Beukema[2]	154	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.

As at December 31, 2016:

- Mr. de Boer holds 1,171,208 ordinary shares in the Company as well as 209,621 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. In 2016, he was awarded 129,727 options at an exercise price of € 6.64 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 8.5 years at December 31, 2016.
- Mr. Beukema holds 300,000 ordinary shares in the Company as well as 197,673 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. In 2016, he was awarded 50,608 options at an exercise price of € 6.64 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 7.5 years at December 31, 2016.

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:

	2016	2015	2014
	(€ in thousands)		
Audit fees	165	193	390
Audit-related fees	39	—	—
Tax fees	—	—	—
All other fees	—	—	—
	204	**193**	**390**

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

On March 27, 2017, the Company announced that it appointed David M. Rodman, MD as Chief Development Strategy Officer. David will join ProQR in April 2017 having previously served in leadership roles with Novartis Institutes for Biomedical Research (NIBR), Vertex Pharmaceuticals, miRagen Therapeutics and Nivalis Therapeutics. Prior to moving to industry in 2005, David had a distinguished academic career, leading the Center for Genetic Lung Diseases at the University of Colorado and directing the Cystic Fibrosis Care, Teaching and Research efforts at the National Jewish Medical and Research Center in Denver, Colorado. During 12 years in industry, David has had global responsibility for driving innovation in the translation of cutting-edge science into transformational new therapies for rare diseases including CF, pulmonary fibrosis, pulmonary artery hypertension and severe immunologic and inflammatory diseases. At Vertex Pharmaceuticals he directed early- and late-stage CF clinical development programs including Kalydeco®, Orkambi® and VX-661. David received a BA in Economics from Haverford College in 1976, an MD from the University of Pennsylvania in 1980 and completed training in Internal Medicine, Pulmonary and Critical Care Medicine at the University of Colorado. He has served as an advisor to the National Institutes of Health, was elected to the American Society for Clinical Investigation and is a Fellow of the American Heart Association.

Exhibit 1.1

ARTICLES OF ASSOCIATION OF:

ProQR Therapeutics N.V.
having its official seat in Leiden, the Netherlands,

as per 22 June 2016.

CONTENTS:

A fair English translation of the complete text of the articles of association of ProQR Therapeutics N.V., as they read after amendment, executed by notarial deed on 22 June 2016 before J.J.C.A. Leemrijse, civil law notary in Amsterdam.

In preparing the attached document, an attempt has been made to translate as literally as possible without jeopardising the overall continuity of the text. Inevitably, however, differences may occur in translation, and if they do, the Dutch text will by law govern.

In the attached document, Dutch legal concepts are expressed in English terms and not in their original Dutch terms; the concepts concerned may not be identical to concepts described by the English terms as such terms may be understood under the laws of other jurisdictions.

DEFINITIONS AND INTERPRETATION

1.1 In these articles of association the following definitions shall apply:

Article	An article of these articles of association.
CEO	The Company's chief executive officer.
Chairman of the Supervisory Board	The chairman of the Supervisory Board.
Class Meeting	The meeting of holders of shares of a certain class.
Company	The company to which these articles of association pertain.
DCC	The Dutch Civil Code.
General Meeting	The Company's general meeting of shareholders.
Group Company	An entity or company which is organisationally connected with the Company in an economic unit within the meaning of Section 2:24b DCC.
Indemnified Officer	A current or former Managing Director or Supervisory Director.
Management Board	The Company's management board.
Management Board Rules	The internal rules applicable to the Management Board, as drawn up by the Management Board.
Managing Director	A member of the Management Board.
Meeting Rights	With respect to the Company, the rights attributed by law to the holders of depository receipts issued for shares with a company's cooperation, including the right to attend and address a General Meeting.
Non-Distributable Equity	The part of the Company's equity that is formed by the paid up and called up part of its capital and the reserves which it must maintain by law.
Person with Meeting Rights	A shareholder, a usufructuary or pledgee with voting rights.
Preferred Distribution	A distribution on the preferred shares for an amount equal to the Preferred Interest Rate calculated over the aggregate amount paid up on those preferred shares, whereby: a. any amount paid up on those preferred shares (including as a result of an issue of preferred shares) during the financial year (or the relevant part thereof) in respect of which the distribution is made shall only be taken into account proportionate to the number of days that elapsed during that financial year (or the relevant part thereof) after those preferred shares were paid up;

b. any reduction of the aggregate amount paid-up on preferred shares during the financial year (or the relevant part thereof) in respect of which the distribution is made shall be taken into account proportionate to the number of days that elapsed during that financial year (or the relevant part thereof) until such reduction of the aggregate amount paid-up on preferred shares was effected; and

c. if the distribution is made in respect of part of a financial year, the amount of the distribution shall be proportionate to the number of days that elapsed during that part of the financial year.

Preferred Interest Rate The mathematical average, calculated over the financial year (or the relevant part thereof) in respect of which a distribution is made on preferred shares, of the EURIBOR interest rate for loans with a maturity of twelve months as published by Thomson Reuters, plus a margin not exceeding five hundred basis points (500bps) to be determined by the Management Board each time when preferred shares are issued without preferred shares already forming part of the Company's issued share capital.

Registration Date The twenty-eighth day prior to the date of a General Meeting.

Simple Majority More than half of the votes cast.

Subsidiary A subsidiary within the meaning of Section 2:24a DCC, including:

a. an entity in whose general meeting the Company or one or more of its Subsidiaries can exercise, whether or not by virtue of an agreement with other parties with voting rights, individually or collectively, more than half of the voting rights; and

b. an entity of which the Company or one or more of its Subsidiaries are members or shareholders and can appoint or dismiss, whether or not by virtue of an agreement with other parties with voting rights, individually or collectively, more than half of the managing directors or of the supervisory directors, even if all parties with voting rights cast their votes.

Supervisory Board	The Company's supervisory board.
Supervisory Board Rules	The internal rules applicable to the Supervisory Board, as drawn up by the Supervisory Board.
Supervisory Director	A member of the Supervisory Board.
Website	The Company's website.

1.2 References to "shares" or "shareholders" are to any class of shares or to the holders thereof, respectively.

1.3 References to statutory provisions are to those provisions as they are in force from time to time.

1.4 Terms that are defined in the singular have a corresponding meaning in the plural.

1.5 Words denoting a gender include each other gender.

1.6 Except in Articles 7.3, 21.2 and 28.7, the terms "written" and "in writing" include the use of electronic means of communication.

NAME AND SEAT

2.1 The Company's name is ProQR Therapeutics N.V.

2.2 The Company has its corporate seat in Leiden.

OBJECTS

The Company's objects are:

a. to develop, to bring to market and to exploit products and technologies in the field of biotechnology;

b. to research and develop (or to commission the research and development of) patents, know-how and intellectual and industrial property;

c. to make the Company's products available to the patient populations that may benefit from such products and to maintain a suitable pipeline of products that may be beneficial for relevant patient populations;

d. to participate in, to finance, to hold any other interest in and to conduct the management or supervision of other entities, companies, partnerships and businesses;

e. to furnish guarantees, to provide security, to warrant performance in any other way and to assume liability, whether jointly and severally or otherwise, in respect of obligations of Group Companies or other parties; and

f. to do anything which, in the widest sense, is connected with or may be conducive to the matters described above in this Article 3.

SHARES - AUTHORISED SHARE CAPITAL AND DEPOSITORY RECEIPTS

4.1 The Company's authorised share capital amounts to three million euro (EUR 3,000,000).

4.2 The authorised share capital is divided into:

a. thirty-seven million five hundred thousand (37,500,000) ordinary shares; and

b. thirty-seven million five hundred thousand (37,500,000) preferred shares,

each having a nominal value of four eurocents (EUR 0.04).

4.3 The Management Board may resolve that one or more shares are divided into such number of fractional shares as may be determined by the Management Board. Unless specified differently, the provisions of these articles of association concerning shares and shareholders apply mutatis mutandis to fractional shares and the holders thereof, respectively.

4.4 The Company cannot cooperate with the issue of depository receipts for shares in its capital.

SHARES - FORM OF SHARES AND SHARE REGISTER

5.1 All shares are registered shares, provided that the Management Board may resolve that one or more ordinary shares are bearer shares, represented by physical share certificates.

5.2 The Management Board is not required to comply with a request made by a shareholder to convert one or more of his registered shares into bearer shares or vice versa. If the Management Board resolves to grant such a request, the shareholder concerned shall be charged for the costs of such conversion.

5.3 Registered shares shall be numbered consecutively for each class of shares, starting from 1.

5.4 The Management Board shall keep a register setting out the names and addresses of all holders of registered shares and all holders of a usufruct or pledge in respect such shares. The register shall also set out any other particulars that must be included in the register pursuant to Section 2:85 DCC and further such other particulars as the Management Board deems prudent. Part of the register may be kept outside the Netherlands to comply with applicable local law or applicable stock exchange rules.

5.5 Shareholders, usufructuaries and pledgees whose particulars must be set out in the register shall provide the Management Board with the necessary particulars in a timely fashion. Any consequences of a failure to notify such particulars or to notify the correct particulars shall be borne by the relevant party.

5.6 All notifications may be sent to Persons with Meeting Rights in respect of registered shares at the addresses set out in the register.

5.7 If the Management Board has resolved that one or more ordinary shares are bearer shares, share certificates shall be issued for such bearer shares in such form as the Management Board may determine. Share certificates may represent one or more bearer shares. Each share certificate shall be signed by or on behalf of a Managing Director.

5.8 The holder of a bearer share that was lost may request the Company to provide a duplicate share certificate for such bearer share. The Company shall only provide such duplicate:

a. if the party making the request can demonstrate, to the satisfaction of the Management Board, that such party is indeed entitled to receive such duplicate; and

b. after having published the request on the Website for a period of four weeks without any objection to such request having been received by the Company within that period.

5.9 If an objection as referred to in Article 5.8 paragraph b. has been received by the Company in a timely fashion, the Company shall only provide the duplicate to the party who requested such duplicate after having been provided with a copy of a binding advice or court order to provide such duplicate, without the Company being required to investigate the competence of the relevant arbitrators or court, as the case may be, or the validity of such binding advice or judgment, as the case may be.

5.10 Upon a duplicate of a share certificate for a bearer share having been provided by the Company, such duplicate shall replace the original share certificate and no rights can be derived from the share certificate thus replaced.

SHARES - ISSUE

6.1 Shares can be issued pursuant to a resolution of the General Meeting or of another body authorised by the General Meeting for this purpose for a specified period not exceeding five years. When granting such authorisation, the number of shares that may be issued must be specified. The authorisation may be extended, in each case for a period not exceeding five years. Unless stipulated differently when granting the authorisation, the authorisation cannot be revoked. For as long as another body has been authorised to issue shares, the General Meeting shall not have this authority.

6.2 Article 6.1 applies mutatis mutandis to the granting of rights to subscribe for shares, but does not apply in respect of issuing shares to a party exercising a previously acquired right to subscribe for shares.

6.3 The Company may not subscribe for shares in its own capital.

SHARES - PRE-EMPTION RIGHTS

7.1 Upon an issue of shares, each holder of ordinary shares shall have a pre-emption right in proportion to the aggregate nominal value of his ordinary shares. Preferred shares do not carry pre-emption rights.

7.2 In deviation of Article 7.1, holders of ordinary shares do not have pre-emption rights in respect of an issue of:

a. preferred shares;

b. ordinary shares against non-cash contribution; or

c. ordinary shares to employees of the Company or of a Group Company.

7.3 The Company shall announce an issue with pre-emption rights and the period during which those rights can be exercised in the State Gazette and in a daily newspaper with national distribution, unless all shares are registered shares and the announcement is sent in writing to all shareholders at the addresses submitted by them.

7.4 Pre-emption rights may be exercised for a period of at least two weeks after the date of announcement in the State Gazette or after the announcement was sent to the shareholders.

7.5 Pre-emption rights may be limited or excluded by a resolution of the General Meeting or of the body authorised pursuant to Article 6.1, if that body was authorised by the General Meeting for this purpose for a specified period not exceeding five years. The authorisation may be extended, in each case for a period not exceeding five years. Unless stipulated differently when granting the authorisation, the authorisation cannot be revoked. For as long as another body has been authorised to limit or exclude pre-emption rights, the General Meeting shall not have this authority.

7.6 A resolution of the General Meeting to limit or exclude pre-emption rights, or to grant an authorisation as referred to in Article 7.5, shall require a majority of at least two thirds of the votes cast if less than half of the issued share capital is represented at the General Meeting.

7.7 The preceding provisions of this Article 7 apply mutatis mutandis to the granting of rights to subscribe for shares, but do not apply in respect of issuing shares to a party exercising a previously acquired right to subscribe for shares.

SHARES - PAYMENT

8.1 Without prejudice to Article 8.2, the nominal value of a share and, if the share is subscribed for at a higher price, the difference between these amounts must be paid up upon subscription for that share. However, it may be stipulated that part of the nominal value of a preferred share, not exceeding three quarters thereof, need not be paid up until the Company has called for payment. The Company shall observe a reasonable notice period of at least one month with respect to any such call for payment.

8.2 Parties who professionally place shares for their own account may be allowed by virtue of an agreement to pay up less than the nominal value of the shares subscribed for by them, provided that at least ninety-four percent (94%) of this amount is paid up in cash ultimately upon subscription for those shares.

8.3 Shares must be paid up in cash, except to the extent that payment by means of a contribution in another form has been agreed.

8.4 Payment in a currency that is not a unit of the euro is only permitted with the Company's consent. Where such a payment is made, the payment obligation is satisfied for the amount in euro for which the paid amount can be freely exchanged. The date of the payment determines the exchange rate. The previous sentence does not prejudice the last sentence of Section 2:80a(3) DCC.

SHARES - FINANCIAL ASSISTANCE

9.1 The Company may not provide security, give a price guarantee, warrant performance in any other way or commit itself jointly and severally or otherwise with or for others with a view to the subscription for or acquisition of shares or depository receipts for shares in its capital by others. This prohibition applies equally to Subsidiaries.

9.2 The Company and its Subsidiaries may not provide loans with a view to the subscription for or acquisition of shares or depository receipts for shares in the Company's capital by others, unless the Management Board resolves to do so and the relevant statutory requirements of Section 2:98c DCC are observed.

9.3 The preceding provisions of this Article 9 do not apply if shares or depository receipts for shares are subscribed for or acquired by or for employees of the Company or of a Group Company.

SHARES - OWN SHARES

10.1 The acquisition by the Company of shares in its own capital which have not been fully paid up shall be null and void.

10.2 The Company may only acquire fully paid up shares in its own capital for no consideration or if and to the extent that the General Meeting has authorised the Management Board for this purpose and all other relevant statutory requirements of Section 2:98 DCC are observed.

10.3 An authorisation as referred to in Article 10.2 remains valid for no longer than eighteen months. When granting such authorisation, the General Meeting shall determine the number of shares that may be acquired, how they may be acquired and within which range the acquisition price must be. An authorisation shall not be required for the Company to acquire ordinary shares in its own capital in order to transfer them to employees of the Company or of a Group Company pursuant to an arrangement applicable to them, provided that these ordinary shares are included on the price list of a stock exchange.

10.4 The Company may acquire shares in its own capital for cash consideration or for consideration satisfied in the form of assets. In the case of a consideration being satisfied in the form of assets, the value thereof, as determined by the Management Board, must be within the range stipulated by the General Meeting as referred to in Article 10.3.

10.5 Articles 10.1 through 10.3 do not apply to shares acquired by the Company by universal succession.

10.6 In this Article 10, references to shares include depository receipts for shares.

SHARES - REDUCTION OF ISSUED SHARE CAPITAL

11.1 The General Meeting can resolve to reduce the Company's issued share capital by cancelling shares or by reducing the nominal value of shares by virtue of an amendment to these articles of association. The resolution must designate the shares to which the resolution relates and it must provide for the implementation of the resolution.

11.2 A resolution to cancel shares may only relate to:

a. shares held by the Company itself or in respect of which the Company holds the depository receipts; or

b. all preferred shares, with repayment of the amounts paid up in respect thereof and provided that, to the extent allowed under Articles 34.1 and 35.2, a distribution is made on those preferred shares, in proportion to the amounts paid up on those preferred shares, immediately prior to such cancellation becoming effective, which distribution shall consist of:

i. the total of all Preferred Distributions (or parts thereof) in relation to financial years prior to the financial year in which the cancellation occurs, to the extent that these have not yet been paid as described in Article 35.1; and

ii. the Preferred Distribution calculated in respect of the part of the financial year in which the cancellation occurs, for the number of days that have elapsed during such part of the financial year.

11.3 A resolution of the General Meeting to reduce the Company's issued share capital shall require a majority of at least two thirds of the votes cast if less than half of the issued share capital is represented at the General Meeting.

11.4 If a resolution of the General Meeting to reduce the Company's issued share capital relates to preferred shares, such resolution shall always require the prior or simultaneous approval of the Class Meeting of preferred shares.

SHARES - ISSUE AND TRANSFER REQUIREMENTS

12.1 Except as otherwise provided or allowed by Dutch law, the issue or transfer of a share shall require a deed to that effect and, in the case of a transfer and unless the Company itself is a party to the transaction, acknowledgement of the transfer by the Company.

12.2 The acknowledgement shall be set out in the deed or shall be made in such other manner as prescribed by law.

SHARES - USUFRUCT AND PLEDGE

13.1 Ordinary shares can be encumbered with a usufruct or pledge. Preferred shares can be encumbered with a usufruct, but cannot be pledged. The voting rights attached to preferred shares which are subject to a usufruct, cannot vest in the usufructuary concerned.

13.2 The voting rights attached to an ordinary share which is subject to a usufruct or pledge vest in the shareholder concerned.

13.3 In deviation of Article 13.2, the holder of a usufruct or pledge on ordinary shares shall have the voting rights attached thereto if this was provided when the usufruct or pledge was created.

13.4 Usufructuaries and pledgees without voting rights shall not have Meeting Rights.

TRANSFER RESTRICTIONS

14.1 A transfer of preferred shares shall require the prior approval of the Management Board. A shareholder wishing to transfer one or more preferred shares must first request the Management Board to grant such approval. For the avoidance of doubt, a transfer of ordinary shares is not subject to transfer restrictions under these articles of association.

14.2 The transfer of preferred shares to which the request for approval relates must take place within three months after the approval of the Management Board has been granted or is deemed to have been granted pursuant to Article 14.3.

14.3 The approval of the Management Board shall be deemed to have been granted:

a. if no resolution granting or denying the approval has been passed by the Management Board within three months after the Company has received the request for approval; or

b. if the Management Board, when denying the approval, does not notify the requesting shareholder of the identity of one or more potential acquirers willing to purchase the preferred shares to which the request for approval relates.

14.4 If the Management Board denies the approval and notifies the requesting shareholder of the identity of one or more potential acquirers, the requesting shareholder shall notify the Management Board within two weeks after having received such notice whether:

a. he withdraws his request for approval, in which case the requesting shareholder cannot transfer the preferred shares concerned; or

b. he accepts the potential acquirer(s), in which case the requesting shareholder shall promptly enter into negotiations with the potential acquirer(s) regarding the price to be paid for the preferred shares concerned.

14.5 If the negotiations referred to in Article 14.4 paragraph b. have resulted in an agreement within two weeks after the end of the period referred to in Article 14.4, the preferred shares concerned shall be transferred for the agreed price within three months after such agreement having been reached. However, if the negotiations referred to in Article 14.4 paragraph b. have not resulted in an agreement within two weeks after the end of the period referred to in Article 14.4:

a. the requesting shareholder shall promptly notify the Management Board thereof; and

b. the price to be paid for the preferred shares concerned shall be equal to the value thereof, as determined by one or more independent experts to be appointed by the requesting shareholder and the potential acquirer(s) by mutual agreement.

14.6 If no agreement is reached on the appointment of the independent expert(s) as referred to in Article 14.5 paragraph b. within two weeks after the end of the period referred to in Article 14.5:

a. the requesting shareholder shall promptly notify the Management Board thereof; and

b. the requesting shareholder shall promptly request the president of the district court in whose district the Company has its corporate seat to appoint three independent experts to determine the value of the preferred shares concerned.

14.7 If and when the value of the preferred shares concerned has been determined by the independent expert(s), irrespective of whether he/they were appointed by mutual agreement or by the president of the relevant district court, the requesting shareholder shall promptly notify the Management Board of the value so determined.

14.8 Promptly following the receipt of a notice as referred to in Article 14.7, the Management Board shall request the/each potential acquirer whether he wishes to withdraw from the sale procedure and, if so, to send notice thereof to the Management Board within two weeks, failing which he shall be assumed not to have withdrawn from the sale procedure.

14.9 If no potential acquirer withdraws from the sale procedure in accordance with Article 14.8, the preferred shares concerned shall be transferred for the price determined by the independent expert(s) within three months after the end of the period referred to in Article 14.8. However, if any potential acquirer withdraws from the sale procedure in accordance with Article 14.8, the Management Board:

a. shall promptly inform the requesting shareholder and the other potential acquirer(s), if any, thereof; and

b. shall give the opportunity to each other potential acquirer, if any, to declare to the Management Board and the requesting shareholder, within two weeks, his willingness to acquire the preferred shares that have become available as a result of the withdrawal, for the price determined by the independent expert(s).

14.10 If it appears that all preferred shares concerned can be transferred for a price determined by the independent expert(s), as a result of one or more other potential acquirers having declared his/their willingness to acquire preferred shares that have become available as a result of a withdrawal as described in Article 14.9 paragraph b., such transfer shall take place within three months after the end of the period referred to in Article 14.9 paragraph b. However, if it appears that not all preferred shares concerned can be transferred for a price determined by the independent expert(s) as a result of a withdrawal by one or more potential acquirers:

a. the Management Board shall promptly notify the requesting shareholder thereof; and

b. the requesting shareholder shall be free to transfer all of the preferred shares to which the request for approval relates, provided that the transfer takes place within three months after having received the notice referred to in paragraph a.

14.11 The Company may only be a potential acquirer under this Article 14 with the consent of the requesting shareholder.

14.12 All notices given pursuant to this Article 14 shall be provided in writing.

14.13 The preceding provisions of this Article 14 do not apply if:

a. a shareholder is under a statutory obligation to transfer his preferred shares to a previous holder thereof; or

b. a shareholder transfers preferred shares to the Company, except in the case that the Company acts as a potential acquirer pursuant to Article 14.11.

14.14 In this Article 14 rights to subscribe for preferred shares shall be equated with preferred shares.

MANAGEMENT BOARD - COMPOSITION

15.1 The Company has a Management Board consisting of at least one Managing Director. A Managing Director may be an individual or an entity.

15.2 The Supervisory Board shall determine the number of Managing Directors with due observance of Article 15.1.

15.3 The General Meeting shall appoint the Managing Directors and may at any time suspend or remove any Managing Director. In addition, the Supervisory Board may at any time suspend a Managing Director. A suspension by the Supervisory Board can at any time be lifted by the General Meeting.

15.4 The General Meeting can only appoint a Managing Director upon a nomination by the Supervisory Board. The General Meeting may resolve to render the nomination to be non-binding by a majority of at least two thirds of the votes cast representing more than half of the issued share capital. If a nomination is rendered non-binding, a new nomination shall be made each time by the Supervisory Board. If the nomination comprises one candidate for a vacancy, a resolution concerning the nomination will result in the appointment of the candidate, unless the nomination is rendered non-binding. A second meeting as referred to in Section 2:120(3) DCC shall not be convened.

15.5 At a General Meeting, a resolution to appoint a Managing Director can only be passed in respect of candidates whose names are stated for that purpose in the agenda of that General Meeting or the explanatory notes thereto.

15.6 The Supervisory Board shall elect a Managing Director to be the CEO. The Supervisory Board may remove the CEO, in the sense that the Managing Director so removed shall subsequently continue his term of office as a Managing Director without having the title of CEO.

15.7 A resolution of the General Meeting to suspend or remove a Managing Director shall require a majority of at least two thirds of the votes cast representing more than half of the issued share capital, unless the resolution is passed at the proposal of the Supervisory Board.

15.8 If a Managing Director is suspended and the General Meeting does not resolve to dismiss him within three months from the date of such suspension, the suspension shall lapse.

15.9 Each Managing Director shall retire in accordance with a rotation schedule to be included in the Management Board Rules. A retiring Managing Director can be reappointed immediately, subject to such rotation schedule.

15.10 Where a Managing Director is no longer in office or is unable to act, he may be replaced temporarily by a person whom the Management Board has designated for that purpose and, until then, the other Managing Director(s) shall be charged with the entire management of the Company. Where all Managing Directors are no longer in office or are unable to act, the management of the Company shall be entrusted temporarily to one or more persons designated by the Supervisory Board for that purpose. Without prejudice to the generality of the previous two sentences, a Managing Director shall be considered to be unable to act within the meaning of this Article 15.10 in the case of:

a. him having been ill, or the Company not having been able to contact him, in each case for a period of at least five consecutive days (or such other period as determined by the Supervisory Board on the basis of the facts and circumstances at hand);

b. his suspension; or

c. him having declared to have, or the Supervisory Board having established that he has, a conflict of interests as described in Article 17.6.

MANAGEMENT BOARD - DUTIES AND ORGANISATION

16.1 The Management Board is charged with the management of the Company, subject to the restrictions contained in these articles of association. In performing their duties, Managing Directors shall be guided by the interests of the Company and of the business connected with it.

16.2 The Management Board shall draw up Management Board Rules concerning the organisation, decision-making and other internal matters of the Management Board, with due observance of these articles of association. In performing their duties, the Managing Directors shall observe and comply with the Management Board Rules.

16.3 The Management Board may perform the legal acts referred to in Section 2:94(1) DCC without the prior approval of the General Meeting.

MANAGEMENT BOARD - DECISION MAKING

17.1 Without prejudice to Article 17.5, each Managing Director may cast one vote at a meeting of the Management Board.

17.2 A Managing Director can be represented by another Managing Director holding a written proxy for the purpose of the deliberations and the decision-making of the Management Board.

17.3 Resolutions of the Management Board shall be passed, irrespective of whether this occurs at a meeting or otherwise, by Simple Majority unless the Management Board Rules provide differently.

17.4 Invalid votes, blank votes and abstentions shall not be counted as votes cast.

17.5 Where there is a tie in any vote of the Management Board, the CEO shall have a casting vote, provided the Management Board consists of three or more Managing Directors. If the Management Board consists of two Managing Directors, the Supervisory Board shall decide in case of a tied vote.

17.6 A Managing Director shall not participate in the deliberations and decision-making of the Management Board on a matter in relation to which he has a direct or indirect personal interest which conflicts with the interests of the Company and of the business connected with it. If, as a result thereof, no resolution can be passed by the Management Board, the resolution shall be passed by the Supervisory Board.

17.7 Meetings of the Management Board can be held through audio- or video-communication facilities, unless a Managing Director objects thereto.

17.8 Resolutions of the Management Board may, instead of at a meeting, be passed in writing, provided that all Managing Directors are familiar with the resolution to be passed and none of them objects to this decision-making process. Articles 17.1 and 17.5 apply mutatis mutandis.

17.9 The approval of the Supervisory Board is required for the following resolutions of the Management Board:

a. the making of a proposal to the General Meeting concerning:

i. the issue of shares or the granting of rights to subscribe for shares;

ii. the limitation or exclusion of pre-emption rights;

iii. the granting of an authorisation as referred to in Articles 6.1, 7.5 and 10.2;

iv. the reduction of the Company's issued share capital;

v. the granting of an approval as referred to in Article 17.10;

vi. the making of a distribution from the Company's reserves or of profits;

vii. the determination that all or part of a distribution, instead of being made in cash, shall be made in the form of shares in the Company's capital or in the form of assets;

viii. the amendment of these articles of association;

ix. the entering into of a merger or demerger;

x. the instruction of the Management Board to apply for the Company's bankruptcy; and

xi. the Company's dissolution;

b. calling for a payment as referred to in Article 8.1;

c. the acquisition of shares by the Company in its own capital, including the determination of the value of a non-cash consideration for such an acquisition as referred to in Article 10.4;

d. the granting of an approval for the transfer of preferred shares as referred to in Article 14.1;

e. the drawing up or amendment of Management Board Rules;

f. the performance of the legal acts described in Article 16.3;

g. the charging of amounts to be paid up on shares against the Company's reserves as described in Article 34.7;

h. the making of an interim distribution;

i. the determination of the Company's strategy, including those resolutions that may have a material impact on the Company's strategy;

j. the adoption of the Company's business plan or budget, as well as any material amendment to or material deviation from the prevailing business plan or budget;

k. the sale or disposition of all, or an essential part of, the Company's assets;

l. the issuance or acquisition of shares and of debentures chargeable against the Company or chargeable against a limited partnership (commanditaire vennootschap) or a general partnership (vennootschap onder firma) of which the Company is a fully liable partner;

m. the application for quotation, or withdrawal of quotation, of the shares or debt of the Company on any stock exchange;

n. the entry into or termination of any long-term, material cooperation by the Company or a Subsidiary with another legal entity or partnership;

o. the Company's investment in the capital of another company in an amount equal to at least one-fourth of the issued capital plus the Company's reserves, as reflected on the Company's most recent balance sheet, as well as a material change to such investment;

p. the termination of a significant number of the Company's employees simultaneously or within a short period of time;

q. a significant change in the employment conditions of the Company's employees; and

r. such other resolutions of the Management Board as the Supervisory Board shall have specified in a resolution of the Supervisory Board to that effect and notified to the Management Board.

17.10 The approval of the General Meeting is required for resolutions of the Management Board concerning a material change to the identity or the character of the Company or the business, including in any event:

a. transferring the business or materially all of the business to a third party;

b. entering into or terminating a long-lasting alliance of the Company or of a Subsidiary either with another entity or company, or as a fully liable partner of a limited partnership or partnership, if this alliance or termination is of significant importance for the Company; and

c. acquiring or disposing of an interest in the capital of a company by the Company or by a Subsidiary with a value of at least one third of the value of the assets, according to the balance sheet with explanatory notes or, if the Company prepares a consolidated balance sheet, according to the consolidated balance sheet with explanatory notes in the Company's most recently adopted annual accounts.

17.11 The absence of the approval of the Supervisory Board or the General Meeting of a resolution as referred to in Articles 17.9 or 17.10, respectively, shall result in the relevant resolution being null and void within the meaning of Section 2:14 DCC, but shall not affect the powers of representation of the Management Board or of the Managing Directors.

MANAGEMENT BOARD - COMPENSATION

18.1 The General Meeting shall upon the proposal of the Supervisory Board determine the Company's policy concerning the compensation of the Management Board with due observance of the relevant statutory requirements.

18.2 The compensation of Managing Directors shall be determined by the Supervisory Board with due observance of the policy referred to in Article 18.1.

18.3 The Supervisory Board shall submit proposals concerning arrangements in the form of shares or rights to subscribe for shares to the General Meeting for approval. This proposal must at least include the number of shares or rights to subscribe for shares that may be awarded to the Management Board and which criteria apply for such awards or changes thereto.

MANAGEMENT BOARD - REPRESENTATION

19.1 The Management Board is entitled to represent the Company.

19.2 The power to represent the Company also vests in each Managing Director individually.

19.3 The Management Board may resolve to grant powers of attorney to represent the Company and to determine the scope of such powers of attorney. If a power of attorney is granted to an individual, the Board of Managing Director may grant an appropriate title to such person.

SUPERVISORY BOARD - COMPOSITION

20.1 The Company has a Supervisory Board consisting of at least three Supervisory Directors. A Supervisory Director must be an individual.

20.2 The Supervisory Board shall determine the number of Supervisory Directors with due observance of Article 20.1.

20.3 The General Meeting shall appoint the Supervisory Directors and may at any time suspend or remove any Supervisory Director.

20.4 The General Meeting can only appoint a Supervisory Director upon a nomination by the Supervisory Board. The General Meeting may resolve to render the nomination to be non-binding by a majority of at least two thirds of the votes cast representing more than half of the issued share capital. If a nomination is rendered non-binding, a new nomination shall be made each time by the Supervisory Board. If the nomination comprises one candidate for a vacancy, a resolution concerning the nomination will result in the appointment of the candidate, unless the nomination is rendered non-binding. A second meeting as referred to in Section 2:120(3) DCC shall not be convened.

20.5 Upon the making of a nomination for the appointment of a Supervisory Director, the Supervisory Board shall provide the following information with respect to the candidate:

a. his name, age and profession;

b. the aggregate nominal value of the shares held by him in the Company's capital;

c. his present and past positions, to the extent that these are relevant for the performance of the tasks of a Supervisory Director;

d. the names of any entities of which he is already a supervisory director or a non-executive director; if these include entities that form part of the same group, a specification of the group's name shall suffice.

Each nomination must be supported by reasons. In the case of a reappointment, the manner in which the candidate has fulfilled his duties as a Supervisory Director shall be taken into account.

20.6 At a General Meeting, a resolution to appoint a Supervisory Director can only be passed in respect of candidates whose names are stated for that purpose in the agenda of that General Meeting or the explanatory notes thereto.

20.7 The Supervisory Board shall elect a Supervisory Director to be the Chairman of the Supervisory Board. The Supervisory Board may remove the Chairman of the Supervisory Board, in the sense that the Supervisory Director so removed shall subsequently continue his term of office as a Supervisory Director without having the title of Chairman of the Supervisory Board.

20.8 A resolution of the General Meeting to suspend or remove a Supervisory Director shall require a majority of at least two thirds of the votes cast representing more than half of the issued share capital, unless the resolution is passed at the proposal of the Supervisory Board.

20.9 If a Supervisory Director is suspended and the General Meeting does not resolve to dismiss him within three months from the date of such suspension, the suspension shall lapse.

20.10 Each Supervisory Director shall retire in accordance with a rotation schedule to be included in the Supervisory Board Rules. A retiring Supervisory Director can be reappointed immediately, subject to such rotation schedule.

20.11 Where a Supervisory Director is no longer in office or is unable to act, he may be replaced temporarily by a person whom the Supervisory Board has designated for that purpose and, until then, the other Supervisory Director(s) shall be charged with the entire supervision of the Company. Where all Supervisory Directors are no longer in office or are unable to act, the supervision of the Company shall be entrusted temporarily to one or more persons designated by the General Meeting for that purpose. The last sentence of Article 15.10 applies mutatis mutandis.

SUPERVISORY BOARD - DUTIES AND ORGANISATION

21.1 The Supervisory Board is charged with the supervision of the policy of the Management Board and the general course of affairs of the Company and of the business connected with it. The Supervisory Board shall provide the Management Board with advice. In performing their duties, Supervisory Directors shall be guided by the interests of the Company and of the business connected with it.

21.2 The Management Board shall provide the Supervisory Board with the information necessary for the performance of its tasks in a timely fashion. At least once a year, the Management Board shall inform the Supervisory Board in writing of the main features of the strategic policy, the general and financial risks and the administration and control system of the Company.

21.3 The Supervisory Board shall draw up Supervisory Board Rules concerning the organisation, decision-making and other internal matters of the Supervisory Board and its committees, with due observance of these articles of association. In performing their duties, the Supervisory Directors shall observe and comply with the Supervisory Board Rules.

21.4 The Supervisory Board shall establish a compensation committee, an audit committee and a nomination and governance committee and may establish such other committees as deemed to be appropriate by the Supervisory Board. The Supervisory Board shall draw up the rules which shall govern the composition, duties, organisation and decision-making of these committees.

SUPERVISORY BOARD - DECISION MAKING

22.1 Without prejudice to Article 22.5, each Supervisory Director may cast one vote at a meeting of the Supervisory Board.

22.2 A Supervisory Director can be represented by another Supervisory Director holding a written proxy for the purpose of the deliberations and the decision-making of the Supervisory Board.

22.3 Resolutions of the Supervisory Board shall be passed, irrespective of whether this occurs at a meeting or otherwise, by Simple Majority unless the Supervisory Board Rules provide differently.

22.4 Invalid votes, blank votes and abstentions shall not be counted as votes cast.

22.5 Where there is a tie in any vote of the Supervisory Board, the Chairman of the Supervisory Board shall have a casting vote.

22.6 A Supervisory Director shall not participate in the deliberations and decision-making of the Supervisory Board on a matter in relation to which he has a direct or indirect personal interest which conflicts with the interests of the Company and of the business connected with it. If, as a result thereof, no resolution can be passed by the Supervisory Board, the resolution shall nevertheless be passed by the Supervisory Board.

22.7 Meetings of the Supervisory Board can be held through audio- or video-communication facilities, unless a Supervisory Director objects thereto.

22.8 Resolutions of the Supervisory Board may, instead of at a meeting, be passed in writing, provided that all Supervisory Directors are familiar with the resolution to be passed and none of them objects to this decision-making process. Articles 22.1 and 22.5 apply mutatis mutandis.

SUPERVISORY BOARD - COMPENSATION

The General Meeting may grant a compensation to the Supervisory Directors.

INDEMNITY

Article 24

24.1 The Company shall indemnify each of its Indemnified Officers against:

a. any financial losses or damages incurred by such Indemnified Officer; and

b. any expense reasonably paid or incurred by such Indemnified Officer 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 or former position with the Company, in each case to the fullest extent permitted by applicable law.

24.2 No indemnification shall be given to an Indemnified Officer:

a. if a Dutch court has established, without possibility for appeal, that the acts or omissions of such Indemnified Officer that led to the financial losses, damages, suit, claim, action or legal proceedings as described in Article 24.1 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).

24.3 The Supervisory Board may stipulate additional terms, conditions and restrictions in relation to the indemnification referred to in Article 24.1.

GENERAL MEETINGS – CONVENING AND HOLDING GENERAL MEETINGS

25.1 Annually, at least one General Meeting must be held. This annual General Meeting shall be held within six months after the end of the Company's financial year.

25.2 A General Meeting shall also be held:

a. within three months after the Management Board has considered it to be likely that the Company's equity has decreased to an amount equal to or lower than half of its paid up and called up capital; and

b. whenever the Management Board or the Supervisory Board so decides.

25.3 General Meetings must be held in the place where the Company has its corporate seat in Amsterdam, Rotterdam, Schiphol Airport (municipality Haarlemmermeer), The Hague, Oegstgeest, Leidschendam, Katwijk, Noordwijk or Wassenaar.

25.4 If the Management Board and the Supervisory Board have failed to ensure that a General Meeting as referred to in Articles 25.1 or 25.2 paragraph a. is held in a timely fashion, each Person with Meeting Rights may be authorised by the court in preliminary relief proceedings to convene the General Meeting.

25.5 One or more Persons with Meeting Rights who collectively represent at least ten percent (10%) of the Company's issued share capital may request the Management Board and the Supervisory Board in writing to convene a General Meeting, setting out in detail the matters to be discussed. If neither the Management Board nor the Supervisory Board (each in that case being equally authorised for this purpose) has taken the steps necessary to ensure that the General Meeting could be held within the relevant statutory period after the request, the requesting Person(s) with Meeting Rights may be authorised, at his/their request, by the court in preliminary relief proceedings to convene a General Meeting.

25.6 Any matter of which the discussion has been requested in writing by one or more Persons with Meeting Rights who, individually or collectively, represent at least three percent (3%) of the Company's issued share capital shall be included in the convening notice or announced in the same manner, if the Company has received the substantiated request or a proposal for a resolution no later than on the sixtieth day prior to that of the General Meeting.

25.7 A General Meeting must be convened with due observance of the relevant statutory minimum convening period.

25.8 All Persons with Meeting Rights must be convened for a General Meeting:

a. by means of an announcement published on the Website, where it shall remain directly and permanently available until the General Meeting; and

b. if so required under applicable law, in a daily newspaper with national distribution.

25.9 The holders of registered shares may be convened for a General Meeting by means of letters sent to the addresses of those shareholders in accordance with Article 5.6. The previous sentence does not prejudice the possibility of sending a convening notice by electronic means in accordance with Section 2:113(4) DCC.

GENERAL MEETING - PROCEDURAL RULES

26.1 The General Meeting shall be chaired as follows, and in the following order of priority:

a. if there is a Chairman of the Supervisory Board and he is present at the General Meeting, by the Chairman of the Supervisory Board;

b. by another Supervisory Director present at the General Meeting chosen by the Supervisory Directors present at the General Meeting;

c. if there is a CEO and he is present at the General Meeting, by the CEO;

d. by another Managing Director present at the General Meeting chosen by the Managing Directors present at the General Meeting; or

e. by another person appointed by the General Meeting.

The person who should chair the General Meeting pursuant to paragraphs a. through d. may appoint another person to chair the General Meeting instead of him.

26.2 The chairman of the General Meeting shall appoint another person present at the General Meeting to act as secretary and to minute the proceedings at the General Meeting. Where an official report of the proceedings is drawn up by a civil law notary, no minutes need to be taken. Every Managing Director and Supervisory Director may instruct a civil law notary to draw up such an official report at the Company's expense.

26.3 The chairman of the General Meeting shall decide whether persons other than:

a. Persons with Meeting Rights; and

b. others with a statutory right to attend the General Meeting,

shall be admitted to the General Meeting.

26.4 The holder of a written proxy representing a Person with Meeting Rights at a General Meeting shall only be admitted to the General Meeting if the proxy is determined to be acceptable by the chairman of the General Meeting.

26.5 The Company may direct that any person, before entering a General Meeting, identify himself by means of a valid passport or driver's license and to be submitted to such security restrictions or arrangements as the Company may consider to be appropriate under the given circumstances. Persons who do not comply with these requirements or restrictions may be refused entry to the General Meeting.

26.6 The chairman of the General Meeting has the right to eject any person from the General Meeting if he considers that person to disrupt the orderly proceedings at the General Meeting. In case of ejection, the chairman of the General Meeting may temporarily adjourn the meeting.

26.7 The General Meeting may be conducted in the English language, if so determined by the chairman of the General Meeting.

26.8 The chairman of the General Meeting may limit the amount of time that individuals present at the General Meeting are allowed to take in addressing the General Meeting and the number of questions they are allowed to raise, with a view to ensuring the orderly proceedings at the General Meeting.

GENERAL MEETING - EXERCISE OF MEETING AND VOTING RIGHTS

27.1 Each Person with Meeting Rights has the right to attend, address and, if applicable, vote at a General Meeting, whether in person or represented by the holder of a written proxy. Holders of fractional shares of a certain class, if any, together constituting the nominal value of a share of that class, shall exercise these rights collectively, whether through one of them or through the holder of a written proxy.

27.2 The Management Board may decide that each Person with Meeting Rights is entitled, whether in person or represented by the holder of a written proxy, to participate in, address and, if applicable, vote at the General Meeting by electronic means of communication. For the purpose of applying the preceding sentence it must be possible, by electronic means of communication, for the Person with Meeting Rights to be identified, to observe in real time the proceedings at the General Meeting and, if applicable, to vote. The Management Board may impose conditions on the use of the electronic means of communication, provided that these conditions are reasonable and necessary for the identification of the Person with Meeting Rights and the reliability and security of the communication. Such conditions must be announced in the convening notice.

27.3 The Management Board can also decide that votes cast through electronic means of communication or by means of a letter prior to a General Meeting are considered to be votes that are cast during the General Meeting. These votes shall not be cast prior to the Registration Date.

27.4 For the purpose of Articles 27.1 through 27.3, those who have voting rights and/or Meeting Rights on the Registration Date and are recorded as such in a register designated by the Management Board shall be considered to have voting rights and/or Meeting Rights, as the case may be, irrespective of whoever is entitled to the shares at the time of the General Meeting. Subject to mandatory Dutch law, the Management Board is free to determine, when convening a General Meeting, whether the previous sentence applies.

27.5 As a prerequisite for a Person with Meeting Rights to exercise his Meeting Rights and, if applicable, his voting rights at a General Meeting, that Person with Meeting Rights must notify the Company in writing of his identity and his intention to attend the General Meeting. This notice must be sent after the Registration Date and must be received by the Company ultimately on the seventh day prior to the General Meeting. Persons with Meeting Rights that have not complied with this requirement may be refused entry to the General Meeting.

GENERAL MEETING - DECISION-MAKING

28.1 Each share, irrespective of which class it concerns, shall give the right to cast one vote at General Meetings. For this purpose, fractional shares of a certain class, if any, collectively constituting the nominal value of a share of that class shall be considered to be equivalent to a share of that class.

28.2 No vote may be cast at a General Meeting in respect of a share belonging to the Company or a Subsidiary or in respect of a share for which any of them holds the depository receipts. Usufructuaries and pledgees of shares belonging to the Company or its Subsidiaries are not, however, precluded from exercising their voting rights if the usufruct or pledge was created before the relevant share belonged to the Company or Subsidiary. Neither the Company nor a Subsidiary may vote shares in respect of which it holds a usufruct or a pledge.

28.3 Unless a greater majority is required by law or by these articles of association, all resolutions of the General Meeting shall be passed by Simple Majority.

28.4 Invalid votes, blank votes and abstentions shall not be counted as votes cast. Shares in respect of which an invalid or blank vote has been cast and shares in respect of which an abstention has been made shall be taken into account when determining the part of the issued share capital that is present or represented at a General Meeting.

28.5 Where there is a tie in any vote of the General Meeting, no resolution shall have been passed.

28.6 The chairman of the General Meeting shall decide on the method of voting and may determine the voting procedure at General Meetings.

28.7 The determination made by the chairman of the General Meeting with regard to the results of a vote shall be decisive. However, where the accuracy of the chairman's determination is contested immediately after it has been made, a new vote shall take place if the majority of the General Meeting so requires or, where the original vote did not take place by response to a roll call or in writing, if any party with voting rights present at the General Meeting so requires. The legal consequences of the original vote shall lapse as a result of the new vote.

28.8 The Management Board shall keep a record of the resolutions passed. The record shall be available at the Company's office for inspection by Persons with Meeting Rights. Each of them shall, upon request, be provided with a copy of or extract from the record, at no more than the cost price.

28.9 The Managing Directors and the Supervisory Directors shall, in that capacity, have an advisory vote at General Meetings.

GENERAL MEETING - RESOLUTIONS REQUIRING A PRIOR PROPOSAL

The following resolutions can only be resolved upon by the General Meeting at the proposal of the Management Board:

a. the issue of shares or the granting of rights to subscribe for shares;

b. the limitation or exclusion of pre-emption rights;

c. the granting of an authorisation as referred to in Articles 6.1, 7.5 or 10.2;

d. the reduction of the Company's issued share capital;

e. the granting of an approval as referred to in Article 17.10;

f. a distribution to the holders of ordinary shares;

g. the determination that all or part of a distribution, instead of being made in cash, shall be made in the form of shares in the Company's capital or in the form of assets;

h. the amendment of these articles of association;

i. the entering into of a merger or demerger;

j. the instruction of the Management Board to apply for the Company's bankruptcy; and

k. the Company's dissolution.

CLASS MEETINGS

30.1 A Class Meeting shall be held whenever a resolution of that Class Meeting is required by Dutch law or under these articles of association or whenever the Management Board or the Supervisory Board so decides.

30.2 Without prejudice to Article 30.1, for Class Meetings of ordinary shares, the provisions concerning the convening, drawing up of agendas for, holding of and decision-making at General Meetings shall apply mutatis mutandis.

30.3 For Class Meetings of preferred shares, the following shall apply:

a. Articles 25.3, 25.9, 26.2, 28.1, 28.2 and 28.4 through 28.9 apply mutatis mutandis;

b. a Class Meeting of preferred shares must be convened no later than on the eighth day prior to that of the meeting;

c. a Class Meeting of preferred shares shall appoint its own chairman;

d. all resolutions of a Class Meeting of preferred shares shall be passed by Simple Majority; and

e. where the rules laid down by these articles of association in relation to the convening, location of or drawing up of agendas for Class Meetings of preferred shares have not been complied with, legally valid resolutions may still be passed by the Class Meeting of preferred shares by a unanimous vote at a meeting at which all preferred shares are represented.

30.4 Holders of preferred shares may pass resolutions in writing instead of at a meeting. However, such resolutions may only be passed by a unanimous vote of all holders of preferred shares. The votes may also be cast electronically.

REPORTING – FINANCIAL YEAR, ANNUAL ACCOUNTS AND REPORT OF THE MANAGEMENT BOARD

31.1 The Company's financial year shall coincide with the calendar year.

31.2 Annually, within the relevant statutory period, the Management Board shall prepare the annual accounts and the report of the Management Board and deposit them at the Company's office for inspection by the shareholders.

31.3 The annual accounts shall be signed by the Managing Directors and by the Supervisory Directors. If any of their signatures is missing, this shall be mentioned, stating the reasons.

31.4 The Company shall ensure that the annual accounts, the report of the Management Board and the particulars to be added pursuant to Section 2:392(1) DCC shall be available at its offices as from the convening of the General Meeting at which they are to be discussed. Persons with Meeting Rights are entitled to inspect such documents at that location and to obtain a copy at no cost.

31.5 The annual accounts shall be adopted by the General Meeting.

REPORTING - AUDIT

32.1 The General Meeting shall instruct an auditor as referred to in Section 2:393 DCC to audit the annual accounts. Where the General Meeting fails to instruct an auditor, the Supervisory Board shall be authorised to do so. Where the Supervisory Board also fails to instruct an auditor, the Management Board shall be authorised to do so.

32.2 The instruction may be revoked by the General Meeting and by the body that has granted the instruction; an instruction granted by the Management Board can also be revoked by the Supervisory Board. The instruction can only be revoked for well-founded reasons; a difference of opinion regarding the reporting or auditing methods shall not constitute such a reason.

DISTRIBUTIONS - RESERVES

33.1 The Company may maintain any reserve attached exclusively to the ordinary shares as the Management Board deems to be appropriate.

33.2 The Company shall not attach any reserve to the preferred shares.

DISTRIBUTIONS - ENTITLEMENT AND RESTRICTIONS

34.1 A distribution can only be made to the extent that the Company's equity exceeds the Non-Distributable Equity.

34.2 The preferred shares do not carry any entitlement to distributions other than as described in Articles 11.2, 35.1 and 36.3.

34.3 The parties entitled to a distribution shall be the shareholders, usufructuaries and pledgees, as the case may be, as at a date to be determined by the Management Board for that purpose. This date shall not be earlier than the date on which the distribution was announced.

34.4 Subject to the other provisions of this Article 34, the General Meeting may resolve to make a distribution from the Company's reserves.

34.5 The General Meeting may resolve that all or part of such distribution, instead of being made in cash, shall be made in the form of shares in the Company's capital or in the form of assets.

34.6 The Management Board may resolve to make interim distributions, provided that it appears from interim accounts to be prepared in accordance with Section 2:105(4) DCC that the requirement referred to in Article 34.1 has been met, and taking into account the priority of distributions under Article 35.1.

34.7 The Management Board may resolve to charge amounts to be paid up on shares against the Company's reserves, irrespective of whether those shares are issued to existing shareholders.

34.8 A distribution shall be payable in such currency and on such date as determined by the Management Board.

34.9 A claim for payment of a distribution shall lapse after five years have expired after the distribution was declared.

34.10 For the purpose of calculating any distribution as referred to in this Article 34, shares held by the Company in its own capital shall not be taken into account. No distribution as referred to in this Article 34 shall be made to the Company in respect of shares held by it.

DISTRIBUTIONS - PROFITS

35.1 Subject to Article 34.1, the profits shown in the Company's annual accounts in respect of a financial year shall be appropriated as follows, and in the following order of priority:

a. to the extent that any preferred shares have been cancelled without the payment described in Article 11.2 paragraph b. having been made in full on those preferred shares, any such deficit shall be paid to those who held those preferred shares at the moment of such cancellation becoming effective;

b. to the extent that any Preferred Distribution (or part thereof) in relation to previous financial years has not yet been paid as described in this Article 35.1, any such deficit shall be paid on the preferred shares;

c. the Preferred Distribution shall be paid on the preferred shares in respect of the financial year to which the annual accounts pertain;

d. the Management Board shall determine which part of the remaining profits shall be added to the Company's reserves; and

e. any remaining profits shall be at the disposal of the General Meeting for distribution to the holders of ordinary shares in proportion to the aggregate nominal value of their ordinary shares.

To the extent that the distributions described in paragraphs a. through c. (or part thereof) cannot be paid out of the profits shown in the annual accounts, the deficit shall be paid out of the Company's reserves, subject to Article 34.1.

Distributions on the preferred shares (or to the former holders of preferred shares) as described in this Article 35.1 shall be paid in proportion to the amounts paid up (or formerly paid up) on those preferred shares.

For the avoidance of doubt, the preferred shares shall not carry any entitlement to profits other than as described in this Article 35.1.

35.2 Without prejudice to Article 34.1, a distribution of profits shall be made after the adoption of the annual accounts that show that such distribution is allowed.

35.3 For the purpose of calculating any distribution of profits, shares held by the Company in its own capital shall not be taken into account. No distribution of profits shall be made to the Company in respect of shares held by it.

DISSOLUTION AND LIQUIDATION

36.1 In the event of the Company being dissolved, the liquidation shall be effected by the Management Board under the supervision of the Supervisory Board, unless the General Meeting in its resolution to dissolve the Company decides otherwise.

36.2 To the extent possible, these articles of association shall remain in effect during the liquidation.

36.3 To the extent that any assets remain after payment of all of the Company's debts, those assets shall be distributed as follows, and in the following order of priority:

a. the amounts paid up on the preferred shares shall be repaid on those preferred shares;

b. to the extent that any preferred shares have been cancelled without the payment described in Article 11.2 paragraph b. having been made in full on those preferred shares, any such deficit shall be paid to those who held those preferred shares at the moment of such cancellation becoming effective; and

c. to the extent that any Preferred Distribution (or part thereof) in relation to financial years prior to the financial year in which the distribution referred to in paragraph a. occurs has not yet been paid as described in Article 35.1, any such deficit shall be paid on the preferred shares;

d. the Preferred Distribution shall be paid on the preferred shares calculated in respect of the part of the financial year in which the distribution referred to in paragraph a. occurs, for the number of days that have already elapsed during such part of the financial year; and

e. any remaining assets shall be distributed to the holders of ordinary shares in proportion to the aggregate nominal value of their ordinary shares.

Distributions on the preferred shares (or to the former holders of preferred shares) as described in this Article 36.3 shall be paid in proportion to the amounts paid up (or formerly paid up) on those preferred shares.

36.4 For the purpose of calculating any distribution as referred to in Article 36.3, shares held by the Company in its own capital shall not be taken into account. No distribution as referred to in Article 36.3 shall be made to the Company in respect of shares held by it.

36.5 After the liquidation has been completed, the Company's books, records and other information carriers shall be kept for the period prescribed by law by the person designated for that purpose in the resolution of the General Meeting to dissolve the Company. Where the General Meeting has not designated such a person, the liquidators shall do so.

Exhibit 4.12

Amendment Number 4
To
Exclusive Patent License Agreement
MGH Agreement Number: A212814.04
MGH Case Number: 2562

This Amendment to the Exclusive Patent License Agreement ("Fourth Amendment") is made as of September, 28, 2016 ("Fourth Amendment Effective Date") by and between ProQR Therapeutics III B.V., a public company organized and existing under the laws of The Netherlands and having a place of business at Zernikedreef 9, 2333CK Leiden, The Netherlands ("Company") and The General Hospital Corporation, d/b/a Massachusetts General Hospital, a not-for-profit Massachusetts corporation, with a principal place of business at 55 Fruit Street, Boston, Massachusetts 02114 ("Hospital"), each referred to herein individually as "Party'' and collectively as "Parties."

Recitals

WHEREAS, The predecessor of the Company, by operation of law, acting under its subsequent names ProQR Therapeutics B.V. and ProQR Therapeutics N.V., and Hospital have entered into a May 29, 2012 exclusive patent license agreement, a June 5, 2014 letter agreement; and a November 14, 2014 amendment to said exclusive patent license agreement, and a June 18, 2015 amendment to said exclusive patent license agreement, (when taken together, "Exclusive License Agreement");

WHEREAS, Parties wish to amend the Exclusive License Agreement; and

NOW, THEREFORE, in consideration of the mutual covenants contained herein, the sufficiency of which is hereby acknowledged, Parties hereby agree to the following:

1. Capitalized Terms. Capitalized terms used herein but not defined herein shall have the meanings ascribed to such terms in Exclusive License Agreement.

2. Amendments.

2.1 Section 1.5 shall be deleted and replaced with the following:

"1.5 "Licensed Field" shall mean the diagnosis, prevention, and treatment of diseases and/or conditions in humans, animals, and plants."

2.2 Section 1.13 shall be amended by inserting the phrase "and reasonably allocable to" immediately after the phrase "in connection with" in the first sentence of such Section 1.13.

2.3 Section 1 shall be amended by adding the following new definitions at the end of Section 1:

"1.14 "Primary Field" shall mean all therapeutic indications in the field of Cystic Fibrosis.

1.15 "Secondary Field" shall mean all fields outside of the Primary Field within the License Field."

2.4 Section 2.2 shall be deleted and replace with the following text:

"2.2 Sublicenses. Each sublicense granted hereunder shall be consistent with and comply with all terms of this Agreement, shall incorporate terms and conditions sufficient to enable Company to comply with this Agreement, shall prohibit further sublicense or assignment by a Sublicensee without Hospital consent, which shall not be unreasonably withheld, and shall provide that Hospital is a third party beneficiary thereof. Company shall provide to Hospital a fully signed non-redacted copy of all sublicense agreements and amendments thereto, including all exhibits, attachments and related documents, within thirty (30) days of executing the same. Upon termination of this Agreement or any license granted hereunder for any reason, any sublicenses shall be addressed in accordance with

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "*". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT UNDER RULE 24b-2 OF THE SECURITIES EXCHANGE ACT OF 1934.**

Section 10.7. Any sublicense which is not in accordance with the forgoing provisions shall be null and void."

2.5 A new Section 3.4 shall be added:

"3.4 Company Proposals for Secondary Fields. Within twelve (12) months following the Fourth Amendment Effective Date, Company shall provide Hospital a written research, development, and commercialization plan for the Products it intends to commercialize in each of the Secondary Fields ("Commercialization Plan") that shall specify the resources and timelines required for commercializing Products in such Secondary Fields. Upon receipt of the Commercialization Plan from Company, Hospital shall have thirty (30) days to review and approve the Commercialization Plan. If the Commercialization Plan is reasonably acceptable to Hospital, Hospital and Company will negotiate in good faith for three (3) months following Hospital's approval of Commercialization Plan to enter into a written amendment to Agreement to add time-limited diligence terms for such Secondary Field(s) ("Diligence Amendment"); such time-limited diligence terms for the Secondary Field(s) shall be similar in scope as the diligence terms in Agreement for the Primary Field. For any Secondary Field for which (a) Company does not provide a Commercialization Plan or (b) Parties fail to execute a Diligence Amendment, Parties will execute an amendment to Agreement within thirty (30) days to remove such Secondary Field from the License Field. In such instance, Company shall have no further rights in such Secondary Field, and Hospital shall be free to grant a license to a third party for such Secondary Field."

2.6 Section 2.5 shall be deleted and replace with the following text:

"[RESERVED]".

2.7 Company represents and warrants that it has achieved the diligence requirements listed in Section 3.1(a)(i) – Section 3.1(a)(iv), as amended.

2.8 Sections 3.1(a)(v) and 3.1(a)(vi) shall be deleted and replaced with the following text:

"(v) Enrollment of first subject in a Phase IIb or Phase III trial (whichever is first) on or before December 31, 2018; and

(vi) Regulatory submission in USA on or before December 31, 2024."

2.9 Company shall provide Hospital with a development plan for the commercialization of Products in the Primary Field within thirty (30) days following Fourth Amendment Effective Date.

2.10 Section 3.1(b)(i) shall be deleted and replaced with the following text:

"(i) Following the First Commercial Sale in any country in the License Territory, Company shall itself or through its Affiliates and/or Sublicensees make continuing Sales of the applicable Product or Process in in such country without any elapsed time period of one (1) year or more in which such Sales do not occur, unless such interruption of Sales is due to a restriction by law or as a result of any measure, decision or action of the FDA or other government agency."

2.11 Section 3.2 shall be deleted and replaced with the following text:

"(a) If Company reasonably anticipates that it will fail to meet one of its obligations under Section 3.1, Company will provide written notice to Hospital no later than the last to occur of: (i) three (3) months before the respective obligation is due or (ii) Company becomes aware of the occurrence of circumstances supporting such reasonable anticipation of such failure. Upon written notice from Company, Hospital shall not unreasonably withhold its consent to any revision in such time periods whenever requested in writing by Company provided that such request is either (i) supported by

written evidence of scientific or technical difficulties or delays in clinical studies or regulatory processes that are outside of Company's reasonable control (for example, slower than anticipated enrolment rates, safety or efficacy issues, or manufacturing disruptions or difficulties) or (ii) consistent with a change in strategy (such changes may be required, for example, by changes to standard of care) that is reasonably intended to avoid more substantial delays and to increase the chance of achieving Regulatory Approval and launch of the relevant Licensed Product as efficiently as reasonably possible under then-current circumstances. The revised deadline resulting from any such request shall be subject to all terms of this Agreement including without limitation the right of Hospital to terminate for default pursuant to Section 10.4. Further, if the diligence milestones are extended such that FDA submission contemplated by Section 3.1(a)(vi) happens beyond December 31, 2018, then diligence extension milestone fees as described below will be due upon FDA approval.

(i) 1 year delay $***;

(ii) 2 year delay $*** (i.e., $*** for 2nd year of failure, if $*** for 1st year of extension has already been paid);

(iii) 3 year delay and $*** (i.e., $*** for 3rd year of failure, if $*** for 1st year of extension and $*** for 2nd year of extension has already been paid and

(iv) >3 years, royalty on Net Sales would equal *** in addition to these above payment obligations.

(b) In the event that Company fails to achieve the diligence obligations set forth in Section 3.1 by the deadlines provided therein (as the same may be extended in accordance with this Section 3.2), Hospital may terminate this Agreement but, in making such determination, Hospital shall be guided by the level of continued commitment by Company, its Affiliates and Sublicensees to bring a Product or Process to the market, the ability of Company, its Affiliates and Sublicensees relative to alternate opportunities available to Hospital to bring Products and Processes to the market to benefit patients, and by the level investment of money that Company, its Affiliates and Sublicensees have made in the Products and Processes.

(c) Subject to Section 3.2(b), if Hospital determines that Company has failed to fulfill any of its obligations under Section 3.1 by the deadlines provided therein (as the same may be extended in accordance with this Section 3.2(a), then Hospital may treat such failure as a default and may terminate this Agreement and/or any license granted hereunder in accordance with Section 10.4."

2.12 Section 4.4 of the Agreement shall be deleted and replaced with the following text:

"4.4 Milestone Payments. In addition to the payments set forth in Sections 4.2 and 4.3 above, Company shall pay Hospital milestone payments as follows:

(a) *** within sixty (60) days of enrollment of the first patient in a Phase I/Phase II (whichever is first) trial of the first Product;

(b) *** within sixty (60) days of enrollment of the first patient in a Phase II (b) or Phase III trial (whichever is first) of the first Product; and

(c) *** within sixty (60) days of regulatory approval in the License Territory of any Product for use in the Primary Field;

(d) *** within sixty (60) days of regulatory approval in the License Territory of any Product for use outside of the Primary Field.

(e) Diligence extension milestone payments described in 3.2(a) shall be due within thirty (30) days of regulatory approval."

2.13 Section 7.1 through 7.3 of the Agreement shall be deleted and replaced with the following text:

"7.1 Company Right to Prosecute. Company may, upon notice to Hospital, initiate legal proceedings against an alleged infringer at Company's expense with respect to a claim of a Patent Right in the License Field in the License Territory. Before commencing such action, Company and, as applicable, any Affiliate, shall consult with Hospital, concerning, among other things, Company's standing to bring suit, the advisability of bringing suit, the selection of counsel and the jurisdiction for such action (provided Company must have Hospital's prior written consent with respect to selection of jurisdiction for any action in which Hospital may be joined as a party-plaintiff) and shall use reasonable efforts to accommodate the views of Hospital regarding the proposed action, including without limitation with respect to potential effects on the public interest. Company shall be responsible for all costs, expenses and liabilities in connection with any such action and shall indemnify and hold Hospital harmless therefrom, regardless of whether Hospital is a party-plaintiff, except for the expense of any independent counsel retained by Hospital in accordance with Section 7.5 below.

7.2 Hospital Right to Prosecute. Company shall notify Hospital within three (3) months of the receipt of written inquiry ("Notice Period") by Hospital whether Company intends to prosecute an alleged infringement. If Company notifies Hospital that it intends to so prosecute, Company shall, within three (3) months of its notice to Hospital ("Initiate Period"), either (i) cause such infringement to terminate, or (ii) initiate legal proceedings against the infringer.

In the event that (i) Company notifies Hospital that Company does not intend to prosecute infringement, (ii) Company has not responded within the Notice Period, or (iii) Company has failed to cause infringement to terminate or initiate legal proceedings within the Initiate Period; Hospital will protect its Patent Rights from infringement and prosecute infringers when, in its sole judgment, such action may be reasonably necessary, proper and justified.

7.3 Hospital Joined as Party-Plaintiff. If Company elects to commence an action as described in Section 7.1 above, Hospital shall have, in its sole discretion, the option to join such action as a party-plaintiff. If Hospital is required by law to join such action as a party-plaintiff, Hospital may either, in its sole discretion, permit itself to be joined as a party-plaintiff at the sole expense of Company, or assign to Company all of Hospital's right, title and interest in and to the Patent Right which is the subject of such action (subject to all of Hospital's obligations to the government under law and any other rights that others may have in such Patent Right). If Hospital makes such an assignment, such action by Company shall thereafter be brought or continued without Hospital as a party; provided, however, that Hospital shall continue to have all rights of prosecution and maintenance with respect to Patent Rights and Company shall continue to meet all of its obligations under this Agreement as if the assigned Patent Right were still licensed to Company hereunder."

2.14 Section 10.2 of the Agreement shall be amended by deleting the references therein to "ten (10)" and replacing them with a reference to "thirty (30)".

2.15 Section 10.7 of the Agreement shall be deleted and replaced with the following text:

"10.7 Effect of Termination on Sublicenses. Any sublicenses granted by Company under this Agreement shall provide for termination or assignment to Hospital of Company's interest therein upon termination of this Agreement or upon termination of any license hereunder under which such sublicense has been granted. For each Sublicense that is in effect as of the date of termination of this Agreement, if (i) Company has provided Hospital with notice and a copy of the applicable sublicense agreement in accordance with Section 2.2, (ii) the terms of such Sublicense agreement are in compliance with the requirements of Section 2.2; and (iii) such Sublicensee is in compliance with the obligations and restrictions set forth in such Sublicense and agrees to assume all of Company's applicable obligations under this Agreement, then such Sublicense shall not be terminated due to termination of Agreement provided, however, in no event shall Hospital be obligated to assume any obligations or liabilities to such Sublicensees beyond the licenses granted in this Agreement. For avoidance of doubt, upon such an assumption of each Sublicense, Hospital and Sublicensee of such Sublicense shall enter into a modified form(s) of this Agreement with only such changes as are required to give effect to the terms of this Section 10.7 and this Agreement shall terminate upon the execution and delivery of such new agreement. If a Sublicensee does not agree to assume the obligations of the Company under this Agreement and has not provided notification to Hospital within ninety (90) days of termination of this Agreement that it can fulfill such obligations hereunder, then Hospital shall, at its option, terminate Sublicense with such Sublicensee agreement."

3. Effect of Amendment. Except as otherwise amended hereby, all terms and conditions of the Exclusive License Agreement shall remain in full force and effect as presently written, and the rights, duties, liabilities, and obligations of Parties thereto, as presently constituted, will continue in full effect; provided however, that any breach(es) of any of the terms of the Agreement in existence prior to the Fourth Amendment Effective Date, that are rendered moot by this Amendment, are hereby deemed to be timely cured by the breaching party.

4. No Modification. This Fourth Amendment may not be amended or modified, nor may any provision hereof be waived, except by a written instrument executed by Parties hereto.

5. Counterparts. This Fourth Amendment may be executed in counterparts, each of which when executed shall be deemed to be an original and both of which together shall constitute one and the same document.

IN WITNESS HEREOF, Parties have caused this Fourth Amendment to be executed by their respective duly authorized representatives as of the Fourth Amendment Effective Date.

ProQR Therapeutics III B.V.		The General Hospital Corporation	
By:	_____	By:	_____
Name:	_____	Name:	_____
Title:	_____	Title:	_____

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PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

Lease Agreement

between
TNO and ProQR Therapeutics I B.V.

Zernikedreef 9
2333 CK
Leiden

Period: 1 January 2016 to 31 December 2020 inclusive

[Initials] [Initials]

Key details of Lease Agreement

• Leased Property:	**a part of the Gaubius Building located at Zernikedreef 9, 2333 CK Leiden**
• Lessor:	**The Netherlands Organisation for applied scientific research TNO**
• Lessee:	**ProQR Therapeutics B.V.**
• Rental period:	**5 (five) years**
• Date of commencement:	**1 January 2016**
• First rent payment:	**prior to the date of commencement**
• Option period:	**5 (five) years**
• Notice period:	**1 (one) year**
• Initial rent:	**736,948.00 EUR**
• Turnover tax on rent:	**yes**
• Service costs advance payment: (inc. energy costs)	**503,843.00 EUR**
• Turnover tax on service costs:	**yes**
• Payment period:	**monthly, in advance**
• Rent indexation:	**yes, CPI all households series (2006 = 100)**
• Service costs indexation:	**yes, CPI collectively agreed (CAO) wages (2010 = 100)**
• Bank guarantee:	**yes**
• Manager:	**TNO, Facilities department**
• Special provisions:	**see Article 11**

LEASE AGREEMENT FOR OFFICE PREMISES
and other business premises within the meaning of Section 7:230a of the Dutch Civil Code

Model established by the Real Estate Council (ROZ) on 30 January 2015 and filed with the Clerk of the District Court at The Hague on 17 February 2015 and registered there under number 15/20. Also published on the website www.roz.nl.

This model may only be referred to and utilised if the text that has been filled in, added or modified is clearly recognisable as such. Any additions and amendments should preferably be incorporated under the heading 'Special Provisions'. The Council accepts no responsibility for adverse consequences arising from the use of the text of the model.

THE UNDERSIGNED

1] The Netherlands Organisation for applied scientific research TNO, a legal person within the meaning of Article 3 of the TNO Act, registered in The Hague and having its offices at Anna van Buerenplein 1, 2595 DA The Hague;

Hereinafter referred to as the '**Lessor**' **or 'TNO'**,

registered in the Trade Register of the Chambers of Commerce under number **27376655**

represented by **Mr W. Nagtegaal (COO) and Ms F. Marring (CFO)**

AND

2] ProQR Therapeutics I B.V., registered in Leiden and having its offices at Darwinweg 24, 2333 CR Leiden

hereinafter referred to as the '**Lessee**' **or 'ProQR'**,

registered in the Trade Register of the Chambers of Commerce under number **63634511**

turnover tax number **NL855325811B01**

represented by **Mr D.A. de Boer (Managing Director)**

WHEREAS:

- **The Lessor sent the Lessee an offer for lease (reference: 2015-BIOS-VM-2018) on 29 October 2015;**
- **The Lessor sent the Lessee a revised offer for lease (reference: 2015-BIOS-VM-0234) on 20 November 2015;**
- **The Lessee agreed to the offer for lease on 25 November 2015;**
- **The offer for lease forms the basis for this Lease Agreement.**

HAVE AGREED

The Leased Property, purpose

1.1 The Lessor hereby lets to the Lessee and the Lessee hereby rents from the Lessor the business premises **and 20 parking spaces** (hereinafter the 'Leased Property'), whose address is **Zernikedreef 9, 2333 CK Leiden**, recorded in the land register as **X number 3976** total area approx. **3,216** m² lettable floor space measured according to **Dutch standard NEN-2580**.

The Leased Property is shown in greater detail in the floor plan/drawing added as Annex 1 to this Lease and initialled by the parties. The condition of the Leased Property on the date of transfer is described in the delivery report to be attached as Annex 2 and initialled by the parties.

1.2 The Leased Property shall be designated via or by the Lessee solely for use as **office space, laboratory space, storage, parking area**.

1.3 The Lessee is not permitted to use the Leased Property for any purposes other than those stated in Article 1.2 without the prior written permission of the Lessor.

1.4 The maximum acceptable loading of the floors of the Leased Property shall be **2.5 kN/m²**.

1.5 On signing the Lease the Lessee **has** received a copy of the energy label, as referred to in the Energy Performance (Buildings) Decree as regards the Leased Property.

1.6 If it turns out that the surface area stated in Article 1.1 is incorrect, the parties agree that:
a deviation from the actual size (greater or lesser size) will not affect the rental price.

Terms and Conditions

2.1 The 'GENERAL TERMS AND CONDITIONS FOR LEASE AGREEMENT FOR OFFICE PREMISES' and other commercial premises in the meaning of Section 7:230a Civil Code', filed with the court registry of the District Court at The Hague on 17 February 2015 and registered there under number 15/21, hereinafter referred to as the 'General Terms and Conditions', form part of this Lease. The Parties are cognisant of the contents of these General Terms and Conditions. The Lessee and Lessor have received a copy of these General Terms and Conditions.

2.2 The General Terms and Conditions referred to in Article 2.1 shall apply unless and insofar as this Lease expressly deviates from the same or where application of the same is impossible as regards the Leased Property.

Rental period, renewal and notice

3.1 This Lease enters into effect on **1 January 2016** (hereinafter 'the date of commencement') and has been entered into for a period of **5 (five)** years ending on **31 December 2020**.

3.2 After the period referred to in Article 3.1 has expired, this Lease shall, subject to notice of termination being given by **Lessee or Lessor**, **continue uninterruptedly** in accordance with the Articles 3.3 and 3.4 for **an additional period of 5 (five) years, therefore up to and including 31 December 2025**.

This Lease shall subsequently continue without interruption for **consecutive periods of 5 (five) years**.

3.3 This Lease can be terminated by the Lessee giving notice to the Lessor or by the Lessor giving notice to the Lessee as at the end of the current rental period or, in the case of a Lease for an indefinite duration, at any moment in time, with due observance of a notice period of **1 (one) year**.

The Lessee and the Lessor have agreed a one-off break option after 3 (three) years, for which a notice period of 1 (one) year applies (see Article 11.3).

3.4 Notice of termination must be given by bailiff's writ or by registered letter.

Rent, turnover tax, service costs, rent adjustment, payment obligations, payment period

4.1 The initial rent of the Leased Property on the date of entry is **€ 736,948.00** per annum (in words**: seven hundred and thirty-six thousand nine hundred and forty-eight euros**).

4.2 The parties agree that the Lessor **will** charge the Lessee turnover tax on the amounts payable.
If a Lease is agreed that is not subject to turnover tax, the Lessee shall be liable to make a separate payment to the Lessor in addition to the rent, to compensate for the loss that the Lessor or its legal successor(s) suffer or will suffer because the turnover tax on the capital expenditures and operating expenses is not (or is no longer) deductible. In that case the provisions of Article 19 of the General Terms and Conditions do not apply.

4.3 The parties declare, while referring to Section 11 subsection 1 opening words under b. part 5 of the Turnover Tax Act 1968, that they have agreed to a rental subject to turnover tax. Furthermore, turnover tax will be charged on the payment due from the Lessee for goods and services supplied by or on behalf of the Lessor as laid down in Article 5 of this Lease and Article 18 of the General Terms and Conditions.

By signing this Lease, the Lessee declares that it intends to use or allow the Leased Property to be used for purposes which render it eligible for a full or substantial deduction of turnover tax further to Section 15 of the Turnover Tax Act 1968, this declaration being made in respect of the current agreement and all future agreements with the Lessor and/or its successors.

4.4 The Lessee's financial year runs from **1 January** up to and including **31 December**.

4.5 The rent shall first be adjusted on **1 January 2017** and subsequently at annual intervals on **1 January** in accordance with Articles 17.1 to 17.3 of the General Terms and Conditions.

If the indexation exceeds 3% then only 50% of the excess (above 3%) shall be charged in calculating the adjusted rent.

4.6 The remuneration payable by the Lessee for supplies of goods and services to be provided by or on behalf of the Lessor shall be determined in accordance with Article 18 of the General Terms and Conditions. A system of advance payments is applied to these payments with a later adjustment, as stated in the General Terms and Conditions.

4.7 The Lessee is no longer required to pay turnover tax on the rent if the Leased Property may no longer be leased with turnover tax, even though the parties agreed to this. If this is the case, the compensation for turnover tax set out in Article 19.1 of the General Terms and Conditions will be applicable and this payment will be set in advance in Article 4.8.

4.8. The Lessee's payment obligations consist of the following components:

The following are payable per payment period of 1 calendar months on the date of entry of the Lease:

• the rental charge	**61,412.33 EUR**
• in the event of a Lease subject to turnover tax, the turnover tax due on the rent	**12,896.59 EUR**
• the rent for parking places	**1,666.67 EUR**
• in the event of a Lease subject to turnover tax, the turnover tax due on the rent	**350.00 EUR**
• turnover tax loss due to not being able to deduct turnover tax from the all-in construction costs of the Leased Property. This amount no longer due as per [**.....end date of review period***] due to expiry of review period*] This amount will not be indexed	**n/a**

• advance payment for the remuneration for the supply of goods and services by the Lessor	**26,896.67 EUR**
• with the turnover tax incurred on the same	**5,648.30 EUR**
• advance payment for energy costs	**15,090.25 EUR**
• with the turnover tax incurred on the same	**3,168.95 EUR**
• % of the basic indexed rent due to turnover tax loss of the Lessor on operating costs (not service charges)	**n/a**
total	**127,129.76 EUR**

in words: **one hundred and twenty-seven thousand one hundred and twenty-nine euros and seventy-six euro cents**

4.9 As regards the date of commencement of the Lease, the first payment by the Lessee concerns the period from **1 January 2016** up to and including **31 January 2016** and the amount payable for this first period is **€ 127,129.76**.

The Lessee shall pay this amount on or before **1 January 2016**.

4.10 The periodical payments that the Lessee is to make to the Lessor on the basis of this rental agreement shall be paid in a single amount by means of advance payments in euros, as stated in Article 4.8, and must be paid in full before or on the first day of the period to which the payments relate.

4.11 Unless stated otherwise, all amounts in this Lease and the General Terms and Conditions forming part of these are exclusive of turnover tax.

Costs of providing supplies and services

5.1. The following supplies and services will be provided by or via the Lessor (Manager):

The parties agree that at the start of the lease the supplies and services shall include, without limitation:

Building maintenance

- **Corrective maintenance (daily maintenance of building installations—technical management)**
- **Preventive maintenance (periodic maintenance and checks of building installations)**
- **Garden maintenance**

Use of energy and water

- **Gas**
- **District heating**
- **Electricity**
- **Water**

Provision of consumptive services

- **Company restaurant**
- **Vending machine services**

Risk management

- **Security and surveillance**
- **Prevention / Emergency response procedures / Pest control**
- **Reception**

Cleaning

- **Cleaning (planned and otherwise)**
- **Window cleaning**

Document management

- **Mail processing (delivery services)**

Waste management

- **Waste removal and processing**

Supply of facility and materials

- **Supply of tools**
- **Gases (laboratory materials)**

Facility management

- **Service coordinator, technical services project manager, handyman**

5% (five per cent) administration charge on the cost of supplies and services

The Lessee and the Lessor shall record the supplies and services and the applicable costs in further detail in a separate service agreement.

5.2, After due consultation with the Lessee, the Lessor shall be entitled to alter the nature and scope of the supplies and services referred to in Article 5.1 or to let them lapse.

Securities

6.1 Before the date of commencement the Lessee shall**: arrange to provide a bank guarantee** to the value of **€ n/a**.

ProQR Therapeutics N.V. has filed the declaration of liability for the Lessee as attached in Annex 6.

Manager

7.1 Until the Lessee advises otherwise, the Manager shall be **TNO**.

7.2 Unless agreed otherwise in writing, the Lessee needs to contact the Manager as regards the content of and all further matters regarding this Lease.

7.3 Notice of termination of the Lease must also be sent to the Lessor.

Incentives

8 The parties declare that no incentives have been agreed between the parties other than those stated in this Lease.

Asbestos/Environment

9.1 The Lessee is aware that asbestos has been incorporated into the Leased Property. The fact that the Lessor is not aware of the presence of asbestos in the Leased Property expressly does not imply any guarantee on the part of the Lessor that no asbestos is present.

9.2 The Lessor is not aware that there is contamination in, on or at the Leased Property to such an extent that it would be necessary to take measures pursuant to legislation at the time of signing the Lease. The fact that the Lessor is not aware of the presence of contamination in, on or at the Leased Property at the time of signing the Lease expressly does not imply any guarantee on the part of the Lessor that no contamination is present.

Sustainability/Green Lease

10 The Parties recognise the importance of sustainability and agree to support each other in achieving the jointly formulated objective or the objective to be formulated and to discuss progress on a regular basis.

Special provisions

11.1 Until 1 July 2017 a 'right of first refusal' for extra premises

The Lessee has during the term of the Lease Agreement a right of first refusal in respect of the lease of the business premises of approx. 713 m² lettable floor space becoming available on the ground floor at the Zernikedreef site, on the following conditions:

a) If the Lessor wishes to lease any business premises on the ground floor of Zernikedreef 9 that are or become available, the Lessor shall issue a one-off written offer for lease of these premises to the Lessee.

b) If the Lessee does not give notice of its wish to enter into an additional lease of one or more of these premises within 10 working days of this communication being sent, the Lessor shall be entitled to lease the premises to a third party.

c) If the Lessee exercises its right of first refusal the same lease terms and conditions shall apply to that lease as set out in the lease agreement with reference 2015-BIOS-VM-0237.

d) The Lessee shall pay to the Lessor in respect of the Right of first refusal (for the period from 1 October 2016 until 1 July 2017) the sum of € 250 (two hundred and fifty euros) per calendar month.

11.2 Penalty clause

The Lessee is aware that the premises referred to in Article 11.1 are required to be vacated by the current tenant (Crucell Holland B.V.) no later than 30 June 2017. If for any reason the Lessor does not deliver up such premises to the Lessee in good time, the Lessor shall pay to the Lessee the sum of € 125,000 per month (excluding turnover tax). The Lessor shall pay this amount following receipt of the sum from the current tenant (Crucell Holland B.V.), which is subject to a penalty clause if it has not delivered up the leased property to the Lessor on 30 June 2017. The Lessor shall make efforts to ensure compliance with this agreement with the current tenant.

11.3 Break option

The Lessee and the Lessor have agreed a one-off break option after 3 (three) years (on 1 January 2019). The Lessee is therefore entitled to give notice to terminate its lease of the Leased Property no later than 31 December 2017. In that case, the rental period shall terminate on 31 December 2018.

11.4 State of delivery at start of Lease Agreement

Further to the provisions of Article 3 of the General Terms and Conditions, the Lessee and the Lessor agree that the Leased Property shall be delivered up in its current state, with the following exceptions:

- Depending on the nature of the laboratory activities carried out (containment level), the laboratories shall be delivered up "bacteria-free";
- The Lessor shall carry out cosmetic refurbishment of the entrance hall / meeting rooms / restaurant area. The Lessor shall consult with the Lessee regarding the plans;

- **The Lessor shall investigate the possibilities for improving the cooling facilities in the building by the installation of central duct cooling capable of further reducing the injection temperature of the primary air supply on each floor to approx. 16°C when the outside air temperature is 28°C. This will improve the indoor climate as compared with the current cooling capacity. The result of the reduction in the indoor temperature during warm periods will remain dependent on the volume of heat generated inside the building and climate conditions outside.**

11.5 Renovations by Lessee

- ***Removal of partition walls + office doors***

The Lessee has indicated that it wishes to remove the majority of the partition walls and doors within the office spaces at the Leased Property. The Lessee has also indicated that it wishes to carry out cosmetic refurbishment of the toilets, storage areas, coffee corners and certain parts of the traffic areas. The Lessee and the Lessor have agreed that the Lessee shall be entitled to deliver up the office area, toilets, coffee corners, traffic areas and storage areas "as is" at the end of the lease (see also Article 11.6).

- ***Alteration of laboratories to office space (including open office space)***

The Lessee has indicated that it wishes to remove part of the existing laboratory fittings, partition walls and doors from a number of the laboratory areas that will be leased in order to convert the same into office space (including open office space).

The Lessee has an obligation to convert the laboratory areas that the Lessee has converted to offices back into laboratories on the expiry of the Lease Agreement. At the start of the Lease Agreement it will be decided which category the laboratories that have been converted into office space belong in and this will be recorded in a delivery report. The Lessor may indicate on the expiry date whether it discharges the Lessee from the obligation to convert back.

If the Lessor does enforce the obligation to convert back and wishes the Lessee to convert the laboratory areas that have been converted into office space back into laboratories (categorised according to the delivery report), the Lessor shall deduct the loss of investment for the alterations made by the Lessee (into offices) from the costs for converting back (into laboratories). The Lessor and the Lessee shall determine within 3 months of the commencement of the Lease Agreement the investment costs incurred for the conversion and the period within which these costs will be written down by the Lessee (see also Article 11.6).

11.6 Alterations / facilities

With the exception of structural construction works and/or installation alterations (see also Articles 12.2 and 12.3 of the General Terms and Conditions) the Lessee shall be entitled, subject to prior written approval by the Lessor, to make alterations and/or changes to the Leased Property during the term of the Lease Agreement. The Lessor shall not withhold approval on unreasonable grounds. The Lessor may give approval subject to conditions concerning the state in which the Leased Property must be delivered up on termination of the Lease Agreement. The Lessor shall not be liable to make any payment to the Lessee on termination of the Lease Agreement.

11.7

Further to Article 5 of the Lease Agreement and Articles 11 and 18 of the General Terms and Conditions, the parties agree that the use of common facilities and services and the cost of the same shall be agreed in further detail between the Lessee and the Lessor and recorded in a service agreement.

11.8

The Lessee is aware of the fact that TNO wishes at a later stage to transfer the services and support services to an external party or to the tenants of the building. Agreements will be reached concerning this and once the transfer has taken place the service agreement will be dissolved and only the Lease Agreement will remain in force. It is not yet clear when this will be implemented. Implementation may have consequences for each tenant with respect to the price and substance of the services and support services.

11.9 Separate meters

Further to Article 18.9, the Lessee is aware that the Leased Property does not have its own separate meters (usage meters). The Lessee pays its share of the energy costs in accordance with the m² GFN (Weighed Functional Net surface area) apportionment formula.

Partly at the instigation of the Lessee, the Lessor is having an investigation conducted into a more reasonable apportionment of the energy costs. If a more reasonable charge can be arrived at on the basis of the outcome of this investigation, an interim revision of the advance payment for energy costs will take place on the basis of the outcome of the investigation and following consultation with the Lessee.

11.10 Right to lease in the event of future new build

In the event that the Lessor decides to sell the property it shall introduce the Lessee to the buyer. The Lessor shall inform the buyer as to the Lessee's wishes and interest with respect to any new build development and pass this information to the buyer. The Lessor cannot provide any guarantees in respect of any new build developments that may take place at the site in future.

11.11

Further to Article 20 of the General Terms and Conditions the Lessee and the Lessor agree that the taxes, dues and levies referred to in this Article shall be charged by the Lessor and are included in the rent payable by the Lessee.

11.12 State of delivery on termination of Lease Agreement

Further to Article 22 of the General Terms and Conditions, the laboratories, office spaces and storage areas shall be delivered up by the Lessee empty and broom clean. The Lessee shall also have the laboratories thoroughly cleaned and provide a cleaning certificate.

11.13 Security/Guarantees

The Lessor has assessed the creditworthiness of ProQR Therapeutics I B.V. and estimated this to be low in relation to the amount of the obligations under the Lease Agreement. TNO would prefer to enter into the Lease Agreement with ProQR Therapeutics N.V. The Lessor is aware that ProQR Therapeutics N.V. has filed a declaration of liability for its subsidiaries. This means that there is direct liability between the N.V. and ProQR Therapeutics I and that that N.V. can guarantee the activities of ProQR Therapeutics I B.V. This declaration of liability is attached as an annex to this Lease Agreement, together with a declaration by the N.V. to the Lessor that the N.V. shall inform the Lessor in writing by registered post in good time if the N.V. intends to withdraw the 403 declaration (in accordance with Article 2:403).

Further to Article 6.1 the Lessee and the Lessor agree that for such time as the declaration has not been withdrawn no bank guarantee shall be required.

If the liability or guarantee is withdrawn by the N.V. the Lessor shall further to Article 6.1 of the Lease Agreement and Article 24.1 of the General Terms and Conditions require from ProQR Therapeutics N.V. a bank guarantee addressed to the Lessor in the amount of three months' rent. In this situation, the Lessee shall immediately arrange a bank guarantee from the relevant banking institution conforming to TNO's model bank guarantee.

11.14

The Lessee and the Manager agree that the Lessee shall observe the House Rules. The House Rules, which apply to the entire building of which the Leased Property is a part, shall be included in the service agreement. The Lessor shall be entitled to make reasonable and fair changes to the House Rules and shall inform the Lessee in the event that this takes place.

11.15 Permits

Further to Articles 4.3 and 4.4 of the General Terms and Conditions the Lessee and the Lessor agree that:

- **TNO does not have authorisation for DM-3 activities (activities with microorganisms involving animals held under Class III conditions) as part of its environmental permit (*omgevingsvergunning milieu*);**
- **The GMO (genetically modified organisms) permits must be applied for by the Lessee;**
- **The Opium Act exemption (opiate permit) must be applied for by the Lessee;**
- **The Lessee is not authorised to use TNO's animal testing permit to carry out animal testing;**
- **TNO currently holds a Nuclear Energy Act permit for the isotope laboratory (area 13.35);**
- **The permits for the use of animal by-products for the purpose of education, research and diagnosis must be applied for by the Lessee;**
- **Notification must be given to the Inspectorate SZW (Social Affairs and Employment) under Article 4.94 of the Working Conditions Decree before the Lessee commences intentional work with biological agents in class 2 or higher;**
- **The Lessee is aware of the fact that the permit issued under the Environmental Permits (General Provisions) Act (*wabo-vergunning*) imposes requirements regarding the availability of certain information to the competent authorities.**

  The Lessee shall provide to the Lessor the following details (and any changes to the same):

  - **Name(s) of Biological Safety Officer(s) (BSO);**
  - **Level of BSO responsible**

11.16

Further to Article 1.1 the Lessee and the Lessor agree that with effect from 1 January 2016 the Lessee shall lease 20 (twenty) parking spaces in the parking area beside the Leased Property. With effect from 1 July 2016 this number shall be increased by 27 parking spaces. The Lessor shall therefore charge to the Lessee with effect from 1 July 2016 rent for 47 (forty-seven) parking spaces. The Lessee and the Lessor shall conduct discussions around 1 January each year regarding the number of parking spaces required by the Lessee for that year.

11.17 Lease agreement 2014 F&F 615

The lease agreement with reference 2014 F&F 615 dated 24 July 2014 and the corresponding addendum 1 with reference 2015/BIOS/VM/0051 dated 1 October 2015 cease to apply with effect from 1 January 2016 on signature of this Lease Agreement.

11.18

The lease agreement has been prepared subject to approval by the Executive Board of TNO. Until such time as the parties have set out the full detail of this lease agreement in a lease agreement signed by both the Lessee and the Lessor, it is explicitly agreed that no contractual (or pre-contract) commitment shall exist between the Lessee and the Lessor and no right to occupy and use the designated spaces shall apply.

Thus agreed and signed in **dupl**icate

place	date	place	date
The Hague	**16-12-2015**	**Leiden**	**15-12-2015**

TNO
Mr W. Nagtegaal

[Signature]

(Signature Lessor)

ProQR Therapeutics I B.V.
Mr D.A. de Boer

[Signature]

(Signature Lessee)

place **The Hague** date **18-12-2015**

TNO
Ms F. Marring

[Signature]
……
(Signature Lessor)

Annexes: *)

- ☒ 1 floor plan/drawing of the Leased Property.
- ☒ 2 delivery report (to be added at time of transfer).
- ☒ 3 measurement in accordance with **Dutch standard NEN-2580**
- ☒ 4 energy label.
- ☒ 5 General Terms and Conditions
- ☒ 6 declaration of liability/guarantee by ProQR Therapeutics N.V.
- ☒ 7 extract for the Lessee from the Trade Register of the Chamber of Commerce
- ☒ 8 copy of passport [Lessee's authorised representative].

Lessee[**s***]' separate signature[**s***] confirming receipt of their own copy of the 'GENERAL TERMS AND CONDITIONS FOR LEASE AGREEMENT FOR OFFICE PREMISES' and other premises in the meaning of Section 7:230a Civil Code' as referred to in Article 2.1.

Lessee's signature:

[Signature]

This translation can only be used in combination with and as explanation to the Dutch text. In the event of a disagreement or dispute relating to the interpretation of the English text the Dutch text will be binding. These general terms and conditions are subject to Dutch law.

GENERAL TERMS AND CONDITIONS – LEASE AGREEMENT FOR OFFICE PREMISES

and other business premises within the meaning of Section 7:230a of the Dutch Civil Code

In accordance with the model established by the Real Estate Council (ROZ) on 30 January 2015 and filed with the Clerk of the District Court at The Hague on 17 February 2015 and registered there under number 15/21. Also published on the website www.roz.nl. The Council accepts no responsibility for adverse consequences arising from the use of the text of the model.

Size of the Leased Property
1 Under the Leased Property are also to be understood the installations and facilities present in the Leased Property, insofar as these have not been excluded from the delivery report initialled by the parties to be attached as an annex to this Lease.

Suitability of the Leased Property
2.1 For the question whether facts and circumstances limiting quiet enjoyment under the Lease qualify as a defect in the meaning of Section 7:204 of the Civil Code, it is important what the Lessee could reasonably expect from the Leased Property at the start of the Lease.
2.2 Insofar as the Lessor is aware before signing the Lease of facts and circumstances preventing the use of the Leased Property by the Lessee in accordance with the agreed use, the Lessor shall inform the Lessee thereof.
2.3 The Lessee is obliged to (arrange to) thoroughly inspect the Leased Property before entering into the Lease to verify whether the Leased Property is or can be made suitable by the Lessee for the agreed purpose for which the Lessee wishes to use the Leased Property.

Condition of the Leased Property at the start of the Lease
3.1 The Property will be handed over to and accepted by the Lessee in a good state of repair, unless the parties agree otherwise in writing. If at the start of the Lease, no delivery report is drawn up, by derogation from Section 7:224 subsection 2 of the Civil Code the Lessee has received the Leased Property in good condition, without defects and free of damage.
3.2 The general, structural and technical condition of the Leased Property in which the Lessee accepts the Leased Property at the start of the Lease shall be established by the Lessee and the Lessor in a delivery report as an annex initialled by or on behalf of the parties to be attached to the Lease. This delivery report forms part of the Lease.

(Official) regulations and permits
4.1 Both on and after the date of entry referred to in Article 3.1 of the Lease, the Lessor is responsible for obtaining and maintaining the required permits, licences and consents needed to use the Leased Property as referred to in Article 1.1 of the Lease, notwithstanding the provisions of Article 4.4 and 4.5.
4.2 The costs relating to acquiring the permit, exemption or consent referred to in Article 4.1 and also the costs of alterations to the Leased Property in order to meet the conditions of the permit, licence or consent shall be for the Lessor's expense, without prejudice to the Lessee's maintenance, repair and replacement obligations referred to Article 11.2 and 11.5 with regard to the facilities already forming part of the Leased Property.
4.3 Both on and after the date of concluding the Lease, the Lessee is responsible for obtaining and maintaining all other required permits, licences and consents not falling under Article 4.1 needed to use the Leased Property in accordance with the purpose agreed in Article 1.2 of the Lease for which the Lessee is required to use the Leased Property. This also includes all notifications that the authorities have imposed or will impose as regards the use of the Leased Property in accordance with the agreed use referred to above. The notifications imposed by the authorities referred to above include notifications that are compulsory on the grounds of the most recent Building Decree and the most recent General Rules for Establishments (Environmental Management) Decree (Activities Decree).

4.4 The refusal or revocation of a permit, licence or consent as referred to in Article 4.3 does not constitute a defect, unless the refusal or revocation is the result of actions or failures to act on the part of the Lessor.
4.5 The costs relating to acquiring the permit, licence or consent referred to in Article 4.3 and also the costs of alterations to the Leased Property in order to meet the conditions of the permit, licence or consent shall be for the Lessee's expense, without prejudice to the Lessor's maintenance, repair and replacement obligations referred to Article 11.2 and 11.4 with regard to the facilities already forming part of the Leased Property.

Use
5.1 During the whole term of the Lease, the Lessee shall use the Leased Property actively, entirely, properly and personally exclusively for the purpose stated in the Lease. In this connection, the Lessee shall pay due attention to existing restricted rights, qualitative obligations and any requirements imposed or to be imposed (including requirements relating to the Lessee's business, the use of the Leased Property and everything present within the Leased Property) by the government or utility companies. The Lessee is required to equip the Leased Property with sufficient fixtures and fittings. For the purposes of this Lease, utility companies also include similar companies involved in the supply, transportation and metering of consumption of energy, water etc.
5.2 The Lessee shall act in accordance with the provisions of the law and local by-laws as well as customary practices in relation to lettings and rentals, and instructions issued by the authorities, utility companies and insurers. With regard to work concerning safety, fire prevention and lift technology, the Lessee may only engage companies which the Lessor has approved in advance and which are recognised by the National Centre for Prevention (NCP) and the Netherlands Foundation for Lift Equipment. The Lessor shall not withhold this permission on unreasonable grounds. If it is agreed in the context of supplies and services to be provided by or on behalf of the Lessor that the above-mentioned work is to be arranged by the Lessor, the Lessee must not carry out or arrange for such work to be carried out itself. The Lessee shall at all times comply with the user instructions issued by those companies. The Lessee shall also comply with oral and written instruction issued by or on behalf of the Lessor for the purposes of proper use of the Leased Property and of the internal and external areas, installations and facilities of the building or complex of buildings containing the Leased Property. This includes reasonable instructions regarding maintenance, appearance, noise level, order, fire safety, parking behaviour and proper functioning of the installations with respect to the building or complex of buildings of which the Leased Property forms a part.
5.3 The Lessee must not create any trouble or nuisance while making use of the Leased Property or of the building or complex of buildings containing the Leased Property and shall take due care to see that third parties who are present on its account shall not do the same.
5.4 The Lessee is entitled and has a duty to use the common facilities and services that are or will be available to ensure the proper functioning of the building or complex of buildings to which the Leased Property belongs.
5.5 The Lessor has the right to issue instructions with regard to placing (neon) advertising or signs or modifications and additions desired by the Lessee or other changes visible from the outside, where the Lessor shall not withhold its permission on unreasonable grounds. The Lessor may issue instructions, such as concerning the design, location, dimensions and choice of materials. The Lessee is required to comply with such instructions and those of the competent authorities in relation to modifications or additions made by the Lessee.
5.6 The Lessor has the right for itself, for lessee(s) or third parties to make use of roofs, outer walls, façades, areas not accessible to the public or the Lessee, immovable dependencies within the building or complex of buildings, and also the gardens and grounds in order to install antenna installations or for other purposes. If the Lessor wishes to make use of this right it shall inform the Lessee of this in advance. The Lessor shall take account of the Lessee's interests when exercising this right.
5.7 The Lessor may deny the Lessee access to the Leased Property if the Lessee has not (yet) complied with its obligations under the Lease at the time that it wishes to make use of the Leased Property for the first time. This has no effect on the date of entry of the Lease referred to in Article 3.1 of the Lease and the Lessee's obligations deriving from the Lease.

Sub-letting
6.1 The Lessee may not relinquish the Leased Property as a whole or in part to third parties by letting, sub- letting it or allowing others to use it without the prior written permission of the Lessor, nor shall it transfer the rights conferred by this Lease to a partnership of individuals or a legal entity.
6.2 If the Lessee contravenes Article 6.1, it will be liable to the Lessor for a directly enforceable penalty for each day that the contravention continues, equivalent to two times the daily rental payable by the Lessee at the time, without prejudice to the Lessor's right to have the Lease complied with or to dissolve the Lease on the grounds of breach of contract, and to claim damages.

6.3 The Lessee is permitted to sub-let or grant a right of use to the premises to a group company in the meaning of Section 2:24b of the Civil Code provided that this is consistent with the use referred to in Article 1.2 of the Lease and the sub-lessee/user does not sub-let and/or grant use of the premises to a third party. In the sub-letting agreement, the Lessee shall not derogate from the main lease to the disadvantage of the principal Lease. The foregoing shall not affect the Lessee's obligations under the Lease. The Lessee will remain the single point of contact for the Lessor.

Environment and energy label

7.1 In the event that the state or other authorised bodies have issued guidelines, instructions or directions as regards the submission of waste, whether separately or not, the Lessee and the Lessor are obliged to comply strictly with such instructions. In the event that a party does not comply or only partially complies with this obligation, the defaulting party shall become liable for the financial, criminal or other consequences arising from such failures.

7.2 The Lessee is not permitted:

a. to keep environmentally harmful substances in, on, at or in the immediate vicinity of the Leased Property, including malodorous, inflammable or explosive substances;

b. to use the Leased Property in such a way as to create soil or other environmental contamination.

7.3 The Lessor will not indemnify the Lessee against official orders to carry out an environmental survey regarding the Leased Property or to take measures in the event that contamination is discovered under, in, at or around the Leased Property.

7.4 Insofar as the Lessor is obliged to affix an energy label in the Leased Property, the Lessee shall allow the Lessor to do so without attaching further conditions to this.

7.5 The Lessee and the Lessor are not permitted without the Lessor's and Lessee's prior written permission to make any modifications or additions to the Leased Property that would demonstrably worsen the energy index of the Leased Property stated in the energy label, as referred to in Article 1.5 of the Lease.

Rules of conduct, regulations and prohibitions

8.1 The Lessee must not create any trouble or nuisance or cause damage in, on, at or under the Leased Property or complex of buildings containing the Leased Property. Damage to the Leased Property among other things means the use of means of transport that could damage the floors and walls. The Lessee shall take due care to see that third parties who are present on its account shall not do the same. This also applies to the building or complex of buildings containing the Leased Property.

8.2 The Lessee is not permitted:

a. to exceed the Safe Working Load limit of the floors of the building or the complex of buildings containing the Leased Property as stated in the Lease or structurally permissible;

b. to effect modifications or make additions in, on or at the Leased Property that are in conflict with instructions issued by the authorities or by utility companies, or with the conditions under which the owner of the Leased Property has become the owner of the Leased Property or with other limited rights or which could create a nuisance or obstruction to their peaceful enjoyment.

8.3 The Lessee is not permitted without the Lessor's prior written permission to trespass or allow others to trespass on service and equipment areas, flat areas, roofs, gutters and spaces and areas not intended for general use in the Leased Property or the building or complex of buildings containing the Leased Property or to station means of transportation other than at the places intended for the same.

8.4 With regard to the times and the manner in which loading and unloading takes place, the Lessee shall comply with official regulations or instructions from other competent authorities, as well as the Lessor's reasonable instructions.

8.5 The Lessee shall keep escape routes and emergency doors free at all times in the Leased Property and the building or complex of buildings containing the Leased Property and guarantee accessibility of fire extinguishing facilities.

The Lessor shall also refrain from blocking the said escape routes and emergency doors.

8.6 If the Leased Property includes a lift, moving walkway or escalator or automatic door mechanism or similar facilities, or if the Leased Property is accessible by means of or with the help of one or more of the foregoing facilities or similar facilities, such facilities shall only be used at one's own risk. The Lessee shall be responsible for the proper and skilful use of any technical systems forming part of the Leased Property.

Damage

9.1 The Lessee shall notify the Lessor without delay of any defect and any (imminent) damage arising from that defect or another cause or circumstance. The Lessee shall give the Lessor a reasonable time – given the nature of the defect – to commence with rectification of a defect that is the responsibility of the Lessor.

The Lessee shall confirm this notification, including the reasonable time, to the Lessor as quickly as possible in writing.
9.2 The Lessee shall take appropriate and timely steps to prevent and confine any damage to the Leased Property and to the building or complex of buildings of which the Leased Property forms a part. If the (potential) damage cannot be attributed to the Lessee and the costs of the suitable measures are demonstrable and reasonable, the Lessor shall compensate these costs to the Lessee at the Lessee's request.

Liability
10.1 The Lessee shall be liable to the Lessor for all damage to the Leased Property unless the Lessee proves that no blame should be attached to the Lessee and to individuals for whom the Lessee is responsible.
10.2 The Lessee shall indemnify the Lessor against any fines that the Lessee may incur due to the conduct or negligence of the Lessee.
10.3 The Lessor shall not be liable for any damage resulting from a defect and the Lessee cannot claim any rent reduction and setting-off in case of a defect, subject to the right of set-off referred to in Section 7:206 subsection 3 of the Civil Code.
10.4 The provisions of Article 10.3 do not apply under the following circumstances:
- in the event of damage if a defect is the consequence of a serious culpable failure on the part of the Lessor;
- if the Lessor was aware of a defect on signing the Lease and made no specific arrangements with the Lessee about this;
- if it turns out that the Leased Property is not suitable for the use referred to in Article 1.1 of the Lease on the date of entry referred to in Article 3.1 of the Lease because of circumstances attributable to the Lessor;
- if the Lessor should have been aware of a defect when concluding the Lease and the Lessee could not or should not have been aware of this based on its duty to make enquiries under Article 2.3 or was not required to make any enquiries about this;
- if the Lessor has not observed a reasonable time limit set by the Lessee in writing as referred to in Article 9.1 to make a start on rectifying any defect which is the Lessor's financial responsibility.

Costs of maintenance, repairs and renewals, inspections and tests
11.1 The terms used in the Lease and the general provisions 'maintenance, repair and renewal' are defined as follows:
- maintenance: ensuring that a thing remains in good condition, or at least remains in the condition as it existed on the entry date of the Lease, subject to normal wear and tear;
- repair: returning or replacing a thing in a condition that makes it possible to use that thing again as on the date of entry of the Lease;
- renewal: replacing a thing as a consequence of that thing reaching the end of its technical lifespan.
11.2 The Lessor shall be responsible for the costs of maintenance, repair and renewal work to the Leased Property, as specified in Article 11.4 below. The Lessee shall be responsible for all other maintenance, repair and renewal works, including the costs of inspections and tests at the Leased Property. If the Leased Property forms part of a building or complex of buildings, the above-mentioned provisions shall apply also to the specified costs in relation to the building or complex of buildings containing the Leased Property, such as work on communal systems, spaces and other communal facilities, all this *pro rata*.
11.3 Unless otherwise agreed between the parties, the work specified in Articles 11.2, 11.4 and 11.5 shall be carried out by or on the instructions of the party who is liable to pay for it. The parties shall proceed to have such works carried out in good time.
11.4 The Lessor shall be responsible for the costs of:
a. maintenance, repairs and renewal of structural parts of the Leased Property, such as foundations, columns, beams, structural floors, roofs, flat areas, structural walls, outer walls;
b. maintaining, repairing and renewing the stairs, stair treads, sewage pipes, guttering and external window and door frames unless the Lessee has failed to comply with its obligations on the grounds of Article 11.5 sub k.
c. replacement of components and renewal of systems pertaining to the Leased Property;
d. outside paintwork.
The work specified at a. to d. inclusive shall be the Lessor's financial responsibility, unless the work can be regarded as minor repairs, including small-scale and daily maintenance in the legal sense or work to items not introduced in, on or about the Leased Property by or on behalf of the Lessor.
11.5 The Lessee shall be responsible for the following, in clarification of or, as the case may be, in derogation from or supplementation to Article 11.2:

a. external maintenance insofar as it can be shown to relate to routine repairs including minor and daily maintenance in the legal sense, and internal maintenance other than maintenance as specified in Article 11.4, all without prejudice to the following provisions;
b. maintenance, repair and renewal of switches, lamps, lighting (including luminaires), batteries, interior paintwork, power sockets, door and window hardware, glazing and glass doors, mirrors, windows and other panes;
c. maintenance and repair of roller shutters, venetian blinds, canopies and other awnings;
d. maintenance and repair of the system ceiling, including luminaires, bell systems, sinks, kitchen equipment and sanitary ware;
e. maintenance and repair of pipework and taps/cocks for gas, water and electricity, facilities for the prevention of fire, burglary and theft, with all that forms part of them;
f. maintenance and repair of boundary partitions, gardens and grounds, including pavements;
g. regular and proper maintenance, together with regular testing and certification of all technical systems pertaining to the Leased Property, including the replacement of any small components. This work may only be carried out by contractors approved by the Lessor;
h. all testing and inspection, whether prescribed by the government or not and both regular and occasional, as may reasonably be deemed necessary, in the areas of reliability and safety, and for checking good working order, of the systems (technical or otherwise) pertaining to the Leased Property or the Leased Property's immovable appurtenances; the said testing and inspections shall be carried out on the Lessor's instructions; as far as the costs arising from this are concerned, these shall be governed, as far as possible, by the following provisions in Articles 18.3 to 18.8 inclusive;
i. maintenance, repair and renewal of upholstery, floor coverings and items introduced by or on behalf of the Lessee, whether or not this is done under a provisional estimate provided by the Lessor to the Lessee;
j. attention to cleaning the Leased Property and keeping it clean, both internally and externally, including keeping the windows, roller shutters, venetian blinds, canopies and other awnings, the outside window frames and façades of the Leased Property clean, and the removal of any graffiti left on the Leased Property; k. attention to installation of grease-traps, cleaning and unblocking traps, gutters and all waste and sewage pipes as far as the municipal sewer for the Leased Property, scrubbing of sinks and cleaning out ventilation ducts.

11.6 The Lessee shall be liable for maintaining, repairing and renewing any alterations and additions introduced to the Leased Property by or on behalf of the Lessee.

11.7 If, after having been given due notice, the Lessee neglects maintenance or repair work for which it is liable – or if, in the Lessor's opinion this work has been carried out improperly or poorly – the Lessor shall be entitled to have the works of maintenance, repair or renewal deemed to be necessary carried out at the Lessee's cost and risk.

If the work which should have been done at the Lessee's expense cannot be postponed, the Lessor shall be entitled to carry out that work or have it carried out immediately, at the Lessee's expense.

11.8 The Lessor shall consult with the Lessee, in advance, in relation to works of maintenance, repair and renewal which are the Lessor's liability, as regards the manner in which they should be carried out, as far as possible with the Lessee's interests in mind. If the Lessee asks for these works to be carried out outside normal working hours, the Lessee shall be liable for any extra costs involved.

11.9 The Lessee shall be responsible for the proper and skilful use of the technical systems in the Leased Property. The Lessee shall likewise be responsible for any maintenance of those systems carried out by it or on its instructions. The fact that the maintenance is carried out by a business approved by the Lessor shall not absolve the Lessee from this responsibility.

11.10 If the Lessor and the Lessee agree that the maintenance, repair and renewal work in, on or about the Leased Property or the building or the complex of buildings containing the Leased Property, as specified in Articles 11.2, 11.5 and 11.6, which is the Lessee's responsibility, shall be carried out on the Lessor's instructions rather than the Lessee's, then the associated costs shall be passed on by the Lessor to the Lessee. In some cases the Lessor will conclude maintenance contracts for this work.

Modifications and additions by the Lessee

12.1 The Lessee shall at all times notify the Lessor in writing in due time in advance of any change or addition. This includes but is not limited to all changes that could affect the permits applicable to the Leased Property. The Lessee must ensure that it stipulates that the party that makes the changes and additions waives its right of retention.

12.2 The Lessee is permitted without the Lessor's permission to make modifications and/or additions to the Leased Property that are necessary for the operation of the Lessee's business, provided that the modifications and additions do not involve or affect the structure of the Leased Property and/or the technical facilities forming part of the Leased Property or the complex of buildings containing the Leased Property.

12.3 The Lessee requires the prior written permission of the Lessor for all modifications and additions other than those referred to in Article 12.2.
12.4 The modifications and additions referred to in Article 12.2 do not include modifications and additions to the exterior of the Leased Property, including name signs and advertising of the Lessee. These always require the written permission of the Lessor and the Lessee shall comply with the Lessor's reasonable instructions. The Lessor shall not withhold this permission on unreasonable grounds. Furthermore, the Lessee is not permitted to stick paper over windows and shop displays or otherwise obscure them.
12.5 Before making modifications and/or additions to the Leased Property, the Lessee shall always at its own expense research in detail whether there is asbestos at the site where the modifications and/or additions are to be made. The Lessee shall notify the results of this detailed research to the Lessor and if asbestos is present enter into consultations with the Lessor. The Lessee shall indemnify the Lessor against any possible damage and consequences if the Lessee, if there is asbestos present, proceeds to (arrange to) carry out the said works.
12.6 The Lessee warrants that other users of the building or complex of buildings containing the Leased Property will not experience damage and/or nuisance due to modifications and additions, regardless of whether permission is required and/or has been granted.
12.7 If a permit, licence or consent of a third party is required for a modification or addition, the Lessee shall apply for this and shall comply with all instructions relating to this.
12.8 All expenses associated with modifications and additions and administrative charges are for the Lessee's expense insofar as these are made or incurred under its instructions or on its account.
12.9 Modifications and additions made by the Lessee, whether or not with the permission of the Lessor, do not form part of the Leased Property. The Lessor has no maintenance, repair and renewal obligations regarding such modifications and additions.
12.10 The Lessee shall be liable for damages resulting from modifications and additions introduced into the Leased Property by it or on its behalf.
12.11 The Lessee shall observe reasonable instructions given by the Lessor against and the Lessee shall indemnify the Lessor for claims by third parties for damage sustained because of modifications and facilities introduced by the Lessee.
12.12 The Lessee shall in the event of nuisance, hindrance and/or (potential) damage because of a modification or addition take all measures to reverse the damage and prevent nuisance and hindrance.
12.13 In the event that objects attached by the Lessee in connection with works on the Leased Property or the building or complex of buildings containing the Leased Property have to be temporarily removed, the costs for such removal, any storage and reattaching of those objects shall be for the expense of the Lessee.
12.14 The Lessee is obliged to undo modifications and additions before the end of the Lease and to repair the resulting damage unless the Lessor releases it from this obligation.
12.15 The Lessee shall waive all rights and claims based on unjust enrichment in connection with modifications or additions made by or on behalf of the Lessee that have not been reversed at the end of the Lease, unless the parties agree otherwise in writing.

Maintenance and renovation by the Lessor
13.1 The Lessor shall be permitted to (arrange to) carry out work or inspections in, on or about the Leased Property or the building or complex of buildings containing the Leased Property or the adjacent premises in the context of maintenance, repair and renewal. This shall include the introduction of extra facilities and alterations or work required in connection with (environmental) requirements or measures imposed by the government or other competent authorities.
13.2 If the Lessor wishes to proceed with renovation of the Leased Property, it shall put a proposal for such renovations to the Lessee. A proposal for renovations will be considered reasonable if it is approved by at least 51% of the lessees whose leased premises are affected by the renovations and if such lessees rent at least 70% of the lettable floor area in m2, including vacant property, of the building or complex of buildings containing the Leased Property affected by the proposed renovations. For the calculation of the percentage, the Lessor shall be regarded as Lessee of any un-let but lettable floor area in m2.
13.3 Renovation shall be deemed to include (partial) demolition, replacement new build, additions and alterations to the Leased Property or the building or complex of buildings containing the Leased Property.
13.4 The provisions of Section 7:220, subsections 1, 2 and 3 of the Civil Code shall not be applicable. Renovation and maintenance work to the Leased Property, even if these interfere with the Lessee's business activities, or to the building or complex of buildings containing the Leased Property shall not constitute a defect as far as the Lessee is concerned. The Lessee shall tolerate and allow the Lessor to carry out maintenance and renovation work to the Leased Property or the building or complex of buildings containing the Leased Property. The Lessor shall take reasonable proportionate measures to limit the effect on the peaceful enjoyment of the Leased Property.

13.5 In relation to those parts of the Leased Property of which the Lessee does not enjoy exclusive rights of use, such as communal spaces, lifts, escalators, stairs, stairwells, passages, access points, and/or other immovable appurtenances, the Lessor shall be entitled to alter the appearance and fixtures and fittings thereof and to move these parts of the Leased Property provided that the use referred to in Article 1.2 of the Lease remains possible.

Requests/granting requests

14.1 Every deviation/addition from/to this Lease must be agreed in writing.
14.2 Where any provision of this Lease requires the permission of the Lessor or Lessee, the Lessor or the Lessee shall not unreasonably refuse and/or delay this and such permission will only be deemed to have been provided if given in writing.
14.3 Any permission granted by the Lessor or Lessee is for one time only and is not valid for other or subsequent instances. The Lessor or Lessee is entitled to attach reasonable conditions to its permission.

Changes to the organisation of the Lessee/Lessor

15 The parties are obliged to inform each other on each occasion in writing of intended, relevant changes in their organisation, including the company law structure. The aforementioned communication must reach the other party at a time such that it is able to take all timely measures with regard to the proposed change. These measures are understood to include but are not limited to legal actions such as filing an objection to a proposed legal merger or demerger.

Valuation and viewing of the Leased Property

16.1 If the Lessor wishes to have a valuation of the Leased Property carried out or wishes to proceed with having work carried out in, on or to the Leased Property, the Lessee shall be obliged to provide access to the Lessor or those applying to the Lessee on the Lessor's behalf, and to make facilities available for the work to be carried out.
16.2 In order to carry out the tasks described in Article 16.1, the Lessor and all individuals appointed by it shall be entitled to enter the Leased Property, after consultation with the Lessee, between 07.00 a.m. and 17.30 p.m. on working days. In cases of emergency, the Lessor shall be entitled to enter the Leased Property even without consultation and/or outside the aforesaid times.
16.3 In the event of any proposed letting, sale or auction of the Leased Property, and during the final year before the end of the Lease, the Lessee shall be obliged, on having received prior notification by or on behalf of the Lessor, to provide the opportunity, without deriving any claim from this, for viewings of the Leased Property during at least two working days per week. The Lessee shall allow the usual 'To Let' or 'For Sale' signs or posters to be erected on or about the Leased Property

Adjustments to rental

17.1 The rental review agreed in Article 4.5 of the Lease shall take place on the basis of the adjustment of the monthly price index of the Consumer Price Index (CPI), all households series (2006 = 100), published by Statistics Netherlands (CBS). The adjusted rental is calculated according to the following formula: the adjusted rental is equal to the current rental on the date the rent is adjusted, multiplied by the index figure of the calendar month four calendar months prior to the calendar month in which the rental is altered, and divided by the index figure of the calendar month that is sixteen calendar months prior to the calendar month in which the rental is adjusted.
17.2 The rental shall not be adjusted if the adjustment would lead to a lower rental than the most recently valid figure. In such a case the most recently valid rental will continue to apply until a subsequent indexation of the index point in the calendar month four months prior to the adjustment is higher than the index point of the calendar month four months prior to the calendar month in which the most recent adjustment took place. In this event, the rental adjustment will rely on the index figures for the calendar months stated in the foregoing paragraph.
17.3 The adjusted rental is immediately due and payable, even if the Lessee has not received separate notification of the adjustment.
17.4 Where Statistics Netherlands discontinues publication of its retail price index or where the method of calculating this index is substantially altered, a suitable adjusted or comparable price index shall be used as far as possible. In the event of any dispute, a statement shall be requested from the Director of Statistics Netherlands whose decision shall be binding on both parties. Any costs involved shall be divided equally between the parties.

Costs of supplies and services (service charges)

18.1 In addition to the rental, the Lessee shall be liable for the costs of supply, transportation, metering and usage of water and energy for the Leased Property, including the costs of entering into the relevant contracts and meter rental, and any penalties or fines imposed by the utility companies. The Lessee shall conclude the contracts for supply with the relevant organisations, unless the Leased Property has no separate connection and/or the Lessor arranges this as part of the supplies of goods and services provided under the Lease.
18.2 If the parties have not contracted for any ancillary supplies of goods and services, the Lessee shall arrange for these at its own cost and risk, to the Lessor's satisfaction. In such cases the Lessee shall conclude service contracts, as approved by the Lessor, in relation to the systems forming part of the Leased Property.
18.3 If the parties have agreed that ancillary goods and services will be provided by or on behalf of the Lessor, the Lessor shall establish the payment for these due by the Lessee on the basis of the costs incurred in providing these goods and services together with the relevant administrative work. Insofar as the Leased Property forms part of a building or complex of buildings and the supplies of goods and services also relate to other parts thereof, the Lessor shall determine the proportion of the costs reasonably due by the Lessee for those supplies of goods and services. The Lessor shall not be required to take account of the fact that the Lessee may not use one or more of those supplies of goods and services. If one or more parts of the building or complex of buildings are not in use, the Lessor shall ensure, when fixing the Lessee's share, that it is not higher than it would have been if the whole of the building or complex of buildings had then been in use.
18.4 At the end of the service charges year, the Lessor shall send out to the Lessee a detailed statement for each year within 12 months of the end of the year with a detailed breakdown of the costs of the supplies of goods and services, with information on how these were calculated and, so far as applicable, the Lessee's share of those charges in such a way that the Lessee can independently determine the attribution of the charges itself. The principle is that the Lessor will send the detailed statement within 12 months following the end of the year. If the Lessor is not in a position to provide this statement in due time, the Lessor shall notify this to the Lessee stating reasons. The statutory period of limitations starts after the end of the year to which the service charges relate.
18.5 A statement shall be sent out after the end of the Lease for the period not yet accounted for. This final statement shall be sent out not later than 12 months after the end of the year to which the service charges relate, unless the Lessor is not in a position to provide this statement. The Lessor shall notify this to the Lessee stating reasons. Neither the Lessor nor the Lessee shall be allowed to make any premature claims for set-off.
18.6 If it is apparent from the statement for a period in question, and taking account of advance payments, that the Lessee has paid too little or that the Lessor has received too much, there shall be an additional payment or a repayment within three months after the statement is sent out. A challenge to the accuracy of the statement shall not result in any suspension of this payment obligation.
18.7 The Lessor shall be entitled, after due consultation with the Lessee, to alter the nature and scope of the supplies of goods and services.
18.8 The Lessor shall be entitled to adjust the advance payment due by the Lessee for supplies of goods and services on an interim basis in relation to the anticipated costs, including in the circumstances mentioned in Article 18.7.
18.9 If the supply of gas, electricity, heat and/or (hot) water is included in the supplies of goods and services provided by the Lessor, the Lessor shall be entitled, after due consultation with the Lessee, to adjust the method of ascertaining the usage and the Lessee's share, connected therewith, of the costs of consumption, where individual metering in order to make the actual consumption per user visible is permitted in all cases.
18.10 If the consumption of gas, electricity, heat and/or (hot) water is ascertained by reference to metering equipment and if any dispute arises over the Lessee's share of the consumption costs because of non- functioning or incorrect functioning of those meters, then that share shall be established by a company, to be called in by the Lessor, specialising in the measuring and establishment of gas, electricity, heat and/or (hot) water consumption. This shall also apply in the case of damage, destruction or fraud in relation to the meters, without prejudice to the Lessor's other rights in such cases against the Lessee, such as the right to repair or renew those meters and payment of any losses sustained.
18.11 Except in the case of imputable serious failure, the Lessor shall not be liable for any damage resulting from the non-functioning or the improper supply of goods and services. Likewise the Lessee shall not, in such cases, have any claim for reduction in rental.

Turnover tax
19.1 If the Lessee is not (or no longer) using the Leased Property or causing it to be used for activities entitling deduction of turnover tax and the exception from the exemption to deduct turnover tax from the rental thereby comes to an end, then the Lessee shall no longer be due to pay turnover tax on the rental to

the Lessor or its legal successor(s) but shall be liable, from the date such termination becomes effective, to make a separate payment to the Lessor or its legal successor(s) in addition to the rental, in lieu of turnover tax, which shall compensate the Lessor in full for:
a. the turnover tax on running costs of and investment in the Leased Property which is not, or no longer, deductible by the Lessor or its legal successor(s) as a result of the termination of the option;
b. the turnover tax which the Lessor or its legal successor(s) will have to pay to the Tax and Customs Administration by way of re-calculation as specified in Section 15, subsection 4 of the Turnover Tax Act 1968 or review as specified in Sections 11 to 13, inclusive, of the Turnover Tax (Implementation) Decree 1968, all as a result of the termination of the option;
c. all other losses suffered by the Lessee or its legal successor(s) as a result of termination of the option.
19.2 The financial losses suffered by the Lessor or its legal successor(s) as a result of the termination of the option (as referred to in Article 19.1) shall be paid by the Lessee to the Lessor, or its legal successor(s) regularly along with the regular payments of the rental and shall, with the exception of losses specified in Article 19.1 sub a, be spread over the remaining duration of the current Lease by means of an annuity if possible, but shall be immediately payable in full, in one lump sum, if the Lease is terminated in the meantime for any reason whatever.
19.3 The provisions of Article 19.1 sub b shall not apply if, when the present Lease is concluded, the review period for deductions from turnover tax in relation to the Leased Property has expired.
19.4 If a situation such as that contemplated in Article 19.1 should occur, the Lessor or its legal successor(s) shall inform the Lessee how much has to be paid by the Lessor, or its legal successor(s), to the Tax and Customs Administration and detail the other losses as specified in Article 19.1 sub c. The Lessor and/or its successor(s) shall co-operate if the Lessee wishes to have the statement submitted by the Lessor or its legal successor(s) audited by an independent registered accountant. The costs of this are borne by the Lessee.
19.5 If, in any financial year the Leased Property is not used sufficiently, for the purposes stated in Article 4.3 of the Lease, the Lessee shall advise the Lessor or its legal successor(s) of this, within four weeks after the end of the financial year in question, by means of a signed Lessee's declaration. The Lessee shall send a copy of this declaration to the Tax and Customs Administration within the same period.
19.6 If the Lessee fails to comply with the obligation to notify, as stated in Article 19.5, and/or the obligation to use the Leased Property, as stated in Article 19.8, or if it appears in hindsight that the Lessee proceeded on the basis of any incorrect assumption and the Lessor or its legal successor(s) was/were therefore wrong to charge turnover tax on the rental, then the Lessee shall be in default and the Lessor or its legal successor(s) shall be entitled to recover any resulting financial loss from the Lessee. Such loss shall refer to the full amount of the turnover tax due by the Lessor or its legal successor(s) to the Tax and Customs Administration, together with interest, any fines and further costs and damages. The provisions of this Article are therefore to be understood as providing a compensatory arrangement for those cases in which the option is terminated with retroactive effect, the provisions of Article 19.1 notwithstanding. The extra losses suffered by the Lessor or its legal successor(s) as a result of retrospective impact shall be payable by the Lessee immediately, in full and in one lump sum.
The Lessor or its legal successor(s) shall co-operate if the Lessee wishes to have the statement in relation to these extra losses of the Lessor or its legal successor(s) checked by an independent registered accountant. The costs of this are borne by the Lessee.
19.7 The provisions of Articles 19.1, 19.4 and 19.7 shall also apply in the event of the Lessor and/or its successors incurring any financial loss further to the withdrawal of the option applicable to the parties, where such loss becomes apparent after the date of the termination of the Lease, regardless of whether the rental period has expired. Such loss shall be compensated immediately and in full by the Lessee and/or its legal successors.
19.8 Without prejudice to the other relevant provisions of this Lease, the Lessee shall in any case, subject to the option (as referred to in Article 19.1), use the Leased Property or cause it to be used before the end of the financial year following the financial year in which the Lessee takes on the Lease of the Leased Property.

Other taxes, duties, charges, levies, premiums, dues

20.1 The Lessee shall pay the following, even if the assessments are sent to the Lessor:
a. Immovable Property Tax in relation to the actual usage of the Leased Property and the actual shared use of service spaces, general spaces and communal spaces *pro rata*;
b. environmental levies, including surface water pollution duty, waste water drainage contribution and every other contribution under the heading of environmental protection;
c. betterment levy, or any substitute taxes or levies, such for half of the amount of the assessment. The
Lessor shall notify the Lessee in due time of the receipt of a betterment levy assessment. The Lessor shall if requested contest the assessment in question and include the objections of the Lessee, as far as possible. The Lessee shall compensate the Lessor for half of the reasonably incurred costs in that regard.

d. sewerage charges or sewerage taxes in relation to the actual use of the Leased Property and the actual shared use of service spaces, general spaces and communal spaces *pro rata*;
e. other existing or future taxes, including taxes charged for provisions in public areas as well as flag and advertising taxes, BIZ (business investment zone) levy, municipal land encroachment taxes, charges and other levies and dues:
- in respect of the actual use of the Leased Property;
- in respect of the Lessee's property;
- those which would not have been charged, or not charged to such an extent, if the Leased Property were not being used by the Lessee.

20.2 If any charges, duties or taxes due by the Lessee are collected from the Lessor, these will be repaid by the Lessee to the Lessor on the Lessor's first request within 2 months after this assessment has been paid in full.

Insurance

21.1 If the Lessor or other lessees in the building or complex of buildings containing the Leased Property is charged a higher than normal fire insurance premium for structures, stock or contents in relation to the Leased Property, or the building or complex of buildings containing the Leased Property, because of the nature or characteristics of the trade or profession carried out by the Lessee, then the Lessee shall pay the excess above the normal premium to the Lessor or those other lessees.

21.2 The Lessor and the lessees shall be free to choose their insurance companies, to decide the insurable values and to assess the reasonableness of the premium charged.

21.3 'Normal premium' will be taken to mean the premium which the Lessor or Lessee could stipulate from a well-known and respected insurer for covering the Leased Property or stock and contents against risk of fire at the time directly preceding the conclusion of this Lease, without taking any account of the nature or characteristics of the trade or profession to be carried on by the Lessee in the Leased Property, together with – for the duration of the Lease—any adjustment in the said premium not resulting from an alteration to the nature and extent of the insured risk.

End of the Lease or use

22.1 Unless otherwise agreed in writing, the Lessee shall surrender the Leased Property to the Lessor at the end of the Lease or at the end of use thereof in the condition as described in the delivery report at the start of the Lease, account being taken of any normal wear and tear and ageing.

22.2 If no delivery report has been prepared at the start of the Lease, the Leased Property shall be deemed, subject to proof to the contrary provided by the Lessee at the start of the Lease, to have been handed over in a good state of repair, without defects and free of damage, other than normal wear and tear and ageing, and the Lessee shall return the Leased Property in that condition to the Lessor at the end of the Lease.
The provisions of the final sentence of Section 7:224 subsection 2 of the Civil Code do not apply.

22.3 The Lessee shall in addition to Article 22.2 hand back the Leased Property at the end of the Lease vacant and cleared, free of use and rights of use, properly cleaned and with all keys, key cards and suchlike to the Lessor.

22.4 The Lessee shall be obliged to remove all items it has introduced in, on or about the Leased Property or which were taken over by it from the previous lessee or occupier, all at the Lessee's expense, unless the Lessor states or has stated otherwise at any time. The Lessor shall not be liable to make any payment for items not removed, unless agreed otherwise in writing.

22.5 If the Lessee ends its use of the Leased Property before the end of the Lease, the Lessor shall be entitled to obtain access to and take over possession of the Leased Property at the Lessee's expense, without this constituting a defect.

22.6 All items deemed to have been abandoned by the Lessee through leaving them in the Leased Property when it actually leaves the Leased Property may, at the Lessor's discretion, be removed, sold or destroyed by the Lessor, at the Lessee's expense, without any liability on the Lessor's part.

22.7 The parties shall inspect the Leased Property together in a timely manner before the end of the Lease or the use. A report of this inspection shall be prepared by the parties and shall record the findings in relation to the condition of the Leased Property. This report shall also record which work still has to be done at the Lessee's expense in relation to repairs that proved to be required during the investigation and any maintenance required in hindsight, as well as the manner and the time within which that work will have to be accomplished.

22.8 In the event that the Lessee or Lessor, after having been given every opportunity to do so by means of registered letter, does not co-operate within a reasonable period in the inspection and/or determination of the findings and arrangements in the inspection report, the party which insists on determination shall be

authorised to carry out the inspection in the absence of the defaulting party and to draw up a report that is binding on the two parties and to send the other party a copy of this report without delay.
22.9 The Lessee is required to carry out or to have carried out the works that have been laid down on the basis of the inspection report within the time limit stated in the report, or within a time to be decided by the parties, in a proper manner. In the event that the Lessee continues to fail to comply with its obligations in whole or in part deriving from the report, the Lessor is entitled to have the works carried out itself and to reclaim the costs incurred from the Lessee, without prejudice to the Lessor's entitlement to compensation of further damage and costs.
22.10 The Lessee shall be liable to pay a sum to the Lessor for the time taken up in repairing the Leased Property, counting from the day after the date on which the Lease ends, calculated with reference to the most recently applicable rental and payment for ancillary supply of goods and services, all without prejudice to the Lessor's claim for payment of further damages and reasonable costs.

Payments
23.1 Payment of the rental and all further charges arising in terms of this Lease shall be made in Dutch legal tender not later than on the due dates – without suspension, deduction or set-off against any claim the Lessee has against the Lessor – by payment or transfer to a bank account indicated by the Lessor. The Lessee can only set off a claim if the claim has been determined by the court.
This is without prejudice to the Lessee's right to remedy any defects itself and to deduct the reasonable costs thereof from the rental if the Lessor is in default in remedying those defects. The Lessor shall be free, by means of written intimation to the Lessee, to amend the place or method of payment. The Lessor shall be entitled to decide which outstanding claims under the Lease shall be reduced by any payment received from the Lessee.
23.2 On every occasion when an amount due by the Lessee under this Lease is not paid promptly to the Lessor, there shall, by operation of law, be an immediately payable penalty due by the Lessee to the Lessor, of 1% of the amount due per calendar month (with each part of a month counting as a full month) subject to a minimum of € 300 per month, from the date when the amount became due. The above-mentioned penalty (interest) is not due if the Lessee has submitted a substantiated claim to the Lessor before the due date referred to in Article 23.1 by registered letter and the Lessor has not responded to this materially within 4 weeks of receipt of this letter.

Securities
24.1 As a guarantee for the proper compliance with its obligations under the Lease, the Lessee shall at the latest 2 weeks before the date of entry referred to in Article 3.1 of the Lease or that much earlier as the Lessor states, provide to the Lessor a bank guarantee in a format specified by the Lessor, for the amount stated in the Lease, or pay a security deposit on a bank account designated by the Lessor. This bank guarantee or security deposit shall also apply to any extension of the Lease including any amendments thereto and shall continue for at least six months after the date on which the Leased Property is actually vacated by the Lessee and the Lease has ended. Moreover this bank guarantee or security deposit shall be valid in relation to the Lessee's legal successor(s).
24.2 In the event that the bank guarantee or security deposit is called in and (partly) paid out, the Lessee shall arrange, on the Lessor's first request, to have a new bank guarantee or security deposit issued which fulfils the provisions of Articles 24.1, 24.3 and 24.4 up to the applicable amount immediately prior to the time when the bank guarantee or security deposit was called in.
24.3 Following an upward adjustment of the payment obligation referred to in Article 4.8 of the Lease by a total 15% or more, the Lessee is obliged to immediately arrange to have a new bank guarantee issued, on the Lessor's first request or, if this concerns a security deposit, to make additional payment up to an amount adjusted to reflect the new payment obligation.
24.4 If the security deposit is not validly called in by the Lessor, the Lessor shall refund the security deposit or the remainder of the security deposit on termination of the Lease on a bank account to be designated by the Lessee at the latest six months after the end of the Lease.
If the bank guarantee is not validly called in by the Lessor, the Lessor shall return the bank guarantee on termination of the Lease to an address to be designated by the Lessee at the latest six months after the end of the Lease.
24.5 Insofar as they are applicable, Articles 24.1 up to and including 24.4 apply to other securities.

Joint and several liability

25.1 If more than one natural or legal person or entity is contractually bound as Lessee, they shall always be liable jointly and severally to the Lessor and each of them for all of the obligations arising under the Lease.

Deferment of payment or remission on the Lessor's part to one of the lessees, or an offer to do so, shall affect only that Lessee.
25.2 The obligations under the Lease are joint and several, even as regards heirs and other successors-in- title of the Lessee.

Non-availability at the appropriate time
26.1 If the Leased Property is not available on the date of entry referred to in Article 3.1 of the Lease because it has not been cleared, the previous occupier has not vacated in time or the Lessor has not yet obtained the requisite government permits, the Lessee shall not be liable to pay any rental or service charges until the date when the Leased Property is made available to it, and shall also be entitled to postpone its other obligations and the contractually agreed dates by a corresponding period.
26.2 The Lessor shall not be liable for any losses sustained by the Lessee because of any such delays, unless imputable failure on the Lessor's part can be established.
26.3 An imputable failure as referred to in Article 26.2 also includes a situation where the Lessor does not make efforts to still make the Leased Property available to the Lessee as quickly as possible.
26.4 The Lessee shall not be entitled to demand cancellation of the Lease, unless the delayed handover is caused by an imputable serious failure on the Lessor's part and it is unacceptable that the Lease should be maintained unchanged on grounds of reasonableness and fairness, and the Lessor does not make allowances for the Lessee's reasonable interests.

Apartment rights
27.1 If the building or the complex of buildings containing the Leased Property has been or is split into apartment rights, the Lessee is required to observe the instructions stemming from the deed of the division of the Leased Property and the regulations regarding the use of the Leased Property. The same applies if the building or the complex of buildings is or becomes the property of a co-operative. Having to comply with such instructions does not constitute a defect. The Lessor warrants that the said instructions applicable when the Lease is signed are not in conflict with the Lease.
27.2 The Lessor shall, insofar as this is within its power, not co-operate in drawing up instructions that conflict with the Lease.
27.3 The Lessor shall take due care that the Lessee is provided with the instructions regarding use as intended in Article 27.1.

Costs, default
28.1 In all cases where the Lessor/Lessee issues a warning, notice of default or bailiff's writ to the Lessor/Lessee, or where proceedings are taken against the Lessor/Lessee for compliance with its Lease obligations or vacation of the premises, the Lessor/Lessee shall be obliged to pay to the Lessor/Lessee all costs incurred, both judicial and extrajudicial—except when there is a final court order against the Lessor/Lessee for payment of procedural costs.
The reasonable costs incurred will be established in advance between the parties at a level calculated as follows: 15% on the principal with a maximum of € 25,000 per event excluding court registry fees. In case of legal proceedings, the costs of experts (lawyers, bailiffs, etc.) will be paid by the losing party. Section 6:96, subsections 4 and 6 of the Civil Code, expressly including the reference to the maximum amount to be compensated for extrajudicial costs, therefore does not apply to the parties.
28.2 The Lessor/Lessee shall be in default on the mere expiry of one instalment period.

Penalty clause
29 If the Lessee, after having been duly placed in default by the Lessor, does not comply with the provisions of Articles 5.1, 8, 12.1 and 24.1, the Lessee shall forfeit to the Lessor, insofar as no specific penalty has been agreed, a directly enforceable minimum penalty of € 250 for every calendar day that the Lessee is in default. The foregoing does not affect the Lessor's right to enforce its other rights, including the right to demand compliance and the right to full compensation, insofar as the damage incurred exceeds the penalty that is forfeited.

Personal Data Protection Act
30 If the Lessee is a natural person, the Lessee shall, by entering into and signing this Lease, give permission for the Lessor and the manager of the Leased Property to record and process his/her personal details in a database.

Address for service

31.1 From the date of entry referred to in Article 3.1 of the Lease, all notifications by the Lessor to the Lessee in connection with the performance of this Lease shall be sent to the address of the Leased Property.
31.2,If the Lessee is no longer carrying on its business from the Leased Property, the Lessee undertakes immediately to notify the Lessor of this in writing, at the same time confirming the Lessee's new domicile.
31.3 If the Lessee leaves the Leased Property without providing details of a new domicile to the Lessor, the address of the Leased Property shall continue to operate as the Lessee's domicile.

Complaints
32 The Lessee shall lodge any complaints and requests in writing. This may be done orally in urgent cases. In such cases the Lessee shall confirm the complaint or request as quickly as possible in writing.

Final provision
33 If one part of the Lease or these General Terms and Conditions is void or voidable, this will not affect the validity of the remaining provisions of the Lease or these General Terms and Conditions. In such a case the void or voidable provision(s) shall be substituted, in accordance with the provisions of Section 3:42 of the Civil Code, by provisions as close as legally permissible to what the parties would have agreed if they had been aware of the nullity or voidability.

Exhibit 4.14

LICENSE AGREEMENT

between

Radboudumc

as Licensor,

and

ProQR Therapeutics B.V.

as Licensee

regarding antisense oligonucleotide-based therapy for CEP290-associated LCA

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "*". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT UNDER RULE 24b-2 OF THE SECURITIES EXCHANGE ACT OF 1934.**

THE UNDERSIGNED

1. Stichting Katholieke Universiteit, doing business as the Radboud University Medical Center, a company organised under the laws of the Netherlands, established at Geert Grooteplein Noord 9, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands, registered at the Dutch Chamber of Commerce under number 41055629; (hereinafter referred to as "Radboud" or "Licensor");

AND

2. ProQR Therapeutics B.V., a company organised under the laws of The Netherlands, whose corporate seat is at Utrecht and whose offices are at Darwinweg 24, 2333 CR Leiden, the Netherlands, registered at the Dutch Chamber of Commerce under number 54600790, duly represented by its CEO D. A. de Boer, hereinafter referred to as the "Licensee";

Licensor and Licensee are together referred to as the Parties, and each of them as a Party;

WHEREAS

A. Radboud UMC is a renowned university that has discovered an oligonucleotide for the treatment of CEP290 associated Leber congenital amaurosis or leber.

B. Radboud UMC is the sole rightful owner of the Licensed Patent Applications (as defined below) and as listed in Annex 1 of this Agreement. Radboud has the right to grant a license in respect of the Licensed Patent Application.

C. ProQR Therapeutics is engaged in the development and, subsequent, commercialization of a treatment for several (genetic) diseases. For this purpose, it uses inter alia antisense oligonucleotides.

D. In accordance with the non-binding term sheet between the Parties and subject to the terms and conditions of this Agreement, Licensor hereby agrees to grant Licensee an exclusive license to use certain intellectual property rights, in consideration of Licensee's payment of royalty under this Agreement and further fulfilment of the terms and conditions as set forth in this Agreement.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

NOW HEREBY AGREE AS FOLLOWS

ARTICLE 1. INTERPRETATION

1.1. Unless the context requires otherwise, the following terms and expressions in this Agreement shall have the following meanings:

Annex	:	any annex to this Agreement
Affiliate	:	any entity that controls, is controlled by or is under common control of Licensee. For purposes of this definition only, "control" means (a) to possess, directly or indirectly, the power to direct the management or policies of an entity, whether through ownership of voting securities, by contract relating to voting rights or corporate governance, or (b) to own, directly or indirectly, more than fifty percent (50%) of the outstanding voting rights or other ownership interest of such entity
Agreement	:	this license agreement including any Annexes thereto
Confidential Information	:	all information in relation to this Agreement, the Licensed Patents, the Know-How and the Licensed Products, whether in oral, written, graphic or machine-readable form, including but not limited to know-how, designs and

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		drawings, handbooks, specifications, procedures, formulas, descriptions sufficient to allow consistent duplication, source codes, technical information, reports, data, and any other documentation and information related to all of the foregoing, except such information and data as the Parties agree in writing is not proprietary or confidential. It includes but is not limited to all carriers containing such information, meaning all movable things, such as cd-roms, DVD's, USB-sticks and any other information carriers
Effective Date	:	the day the last Party has executed this Agreement
Field	:	All possible prophylactic and therapeutic uses.
Force Majeure	:	any circumstances the cause of which is not reasonably within the control of the Party claiming force majeure and that affect the performance by it under this Agreement and shall include, without limitation, acts of God, strikes, lockouts or industrial disputes or disturbances, civil disturbances, acts of third parties, wars, riots, blockades, insurrections, epidemics, landslides, lightning, earthquakes, fire, storm, floods, washouts, explosions, the inability to obtain or retain necessary authorisations, permits, easements or rights of way, and compliance with any law or governmental order, rule, regulation or direction, regardless of whether it is later held to be invalid

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Improvement	:	any development or modification related to the Field with respect to the Licensed Products or a part hereof, or relating to the production and/or exploitation thereof, whether or not patented or patentable, that is conceived, reduced to practice, discovered, developed or otherwise made at any time during the term of this Agreement. The term Improvements shall also extend to new oligonucleotide based compounds that may be used in the Field but that fall outside of the claims in the Licensed Patents.
Know-how	:	all factual knowledge and expertise which is accumulated by and/or under the control of Licensor relating to the claims in the Licensed Patents on or before the Effective Date
Licensed Patents	:	the applications for patents, as referred to in Annex 1, and including all further applications, divisionals, continuations, continuations-in-part and/or granted patents ensuing from such patent applications in any country in the Territory
License Period	:	The period starting on the Effective Date and continuing until the expiration of all of the Licensed Patent Applications and all granted patents ensuing form such Applications, unless terminated earlier in accordance with this Agreement
Licensed Product	:	any product(s) that, in whole or in part, (i) absent this Agreement, would infringe one or more Valid Claims of the Licensed Patents in the country of sale or (ii)is manufactured by using any method that, absent this Agreement, would infringe one or more Valid Claims of the Licensed Patentin the country of manufacture

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Net Sales	:	the amount as calculated in accordance with Articles 6.2.
Net Sales Related Royalty	:	*** % (percent) of the Net Sales
Other Field	:	any field other than the Field
Reporting Period	:	each three month period ending March 31, June 30, September 30 and December 31.
Sell (and Sale and Sold as the case may be)	:	to sell or have sold, to lease or have leased, to import or have imported or otherwise to transfer or have transferred a Licensed Product for valuable consideration (in the form of cash or otherwise)
Sublicense Royalty	:	***% (*** percent) of any sublicense revenue, including but not limited to royalties and fair market value of any equity and other instruments received by Licensee from the sub licensees in consideration for the sublicense granted under this Agreement
Territory	:	the entire world
Third Party Royalty	:	royalties to one or more third parties for other licenses necessary for the commercialization of any Licensed Products
Valid Claim	:	any claim of a Licensed Patent that (i) has been granted by a patent granting authority, that is in force, and that has not been surrendered, abandoned, revoked or held invalid or unenforceable by a decision taken by an administrative or civil court in a jurisdiction, or (ii) a pending claim in a Licensed Patent application, with the proviso that any claim that is still pending more than 5 years following the filing date of the (corresponding international) application, shall cease to be a Valid Claim until it becomes a granted claim fulfilling the requirements under (i) above.

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1.2. No provision of this Agreement shall be interpreted adversely against a Party solely because that Party was responsible for drafting that particular provision.

1.3. Words denoting the singular shall include the plural and vice versa. Words denoting one gender shall include another gender.

1.4. The words “include”, “included” or “including” are used to indicate that the matters listed are not a complete enumeration of all matters covered.

1.5. The headings in this Agreement are for construction purposes as well as for reference.

ARTICLE 2. EXCLUSIVE LICENSE

2.1. Licensor grants to Licensee for the duration of the License Period an exclusive license, thus also with the exclusion of Licensor, under the Licensed Patents to develop, make, have made, use, sell, offer for sale and import Licensed Products and practice any methods claimed or covered by the Licensed Patents in the Field in the Territory (the “**Purposes**”).

2.2. The Licensee shall be entitled to grant sub-licences of its rights under this Agreement to any third party, provided that (i) the sub-licence shall include obligations on the sub-licensee that are equivalent to the obligations on the Licensee under this Agreement and (ii) Licensee shall promptly furnish Licensor with a fully signed photocopy of all sublicensing agreements.

2.3. The license granted under this Agreement and any sublicenses granted in accordance with Articles 2.2, shall not include any rights to trade names of Licensor.

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2.4. Licensee agrees that the Licensed Patents shall remain vested solely in Licensor both during License Period and thereafter.

2.5. Licensee shall not use any other intellectual property rights or know-how owned or controlled by Licensor or its Affiliates, unless provided for in this Agreement or a separate license agreement.

2.6. Licensee shall not use the Licensed Patents for any Other Field, unless provided for in a separate license agreement.

2.7. Notwithstanding Articles 2.1 and 3.1, Licensor retains the right to use the Licensed Patents and Know-How for its own internal, non-commercial, academic and research purposes. Licensor shall not publish results without discussing and evaluating the possibility of obtaining IP protection or maintaining such results confidential, if this represents a significant commercial value.

ARTICLE 3. KNOW-HOW

3.1. Licensor grants to Licensee for the duration of the License Period a non-exclusive license, with the right to sub-license in accordance with Article 2.2, to use the Know-How in the Field in the Territory only for the Purposes and subject to the terms and conditions hereof. Licensor will provide to Licensee all relevant documents and/or carriers containing the Know-How or relevant to use the Know-How as soon as reasonably possible after execution of this Agreement, and at least within the term set out in Article 5.1.

3.2. Licensee shall keep the Know-How in confidence and shall not disclose any part thereof to any third party during or after the License Period. Licensee may disclose the Know-How or a part thereof to only those employees that have a need to know, provided that such employees are bound by secrecy and non-use obligations similar to the confidentiality and non-use obligations included in this Agreement on such employees. Licensee shall use its best endeavours to prevent that its current, future and former employees use the Know-How or any part thereof outside of their current and/or

future employment agreement with Licensee. Furthermore, Licensee may disclose the Know-How or part thereof to its advisors, agents and/or sub-contractors and/or sublicensees having a need to know, if and to the extent that such advisors, agents and/or subcontractors and/or sublicensees are bound by secrecy and non-use obligations similar to the confidentiality and non-use obligations included in this Agreement.

3.3. The restrictions on disclosure of the Know-How as stated in this Article 3 do not apply to Know-How which:

(a) Licensee proves to be, or at any time to have come, into the public domain otherwise than through default on the part of i) the Licensee, or ii) its current, future, and former employees; or iii) its advisors, agents and/or sub-contractors and/or sublicensees;

(b) Licensee proves to have lawfully acquired from a third party with good legal title thereto;

(c) Licensee proves is independently developed by Licensee without use, directly or indirectly, of the Know-How and/or the Licensed Patents.

3.4. The restriction upon disclosure of the Know-How shall not apply if Licensee is compelled to disclose Know-How or part thereof by a legally binding order of any court of law, government agency or regulatory or statutory authority which has competent jurisdiction. In such case, Licensee shall consult with Licensor to avoid or limit such disclosure insofar as reasonably possible.

3.5. The provisions of clauses 3.2-3.4 shall remain in force during a period of ten (10) years after any termination or other ending, including but not limited to rescission, of this Agreement.

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ARTICLE 4. DILIGENCE REQUIREMENTS

4.1. Licensee will use reasonable efforts to commercialize the Licensed Patents into Licensed Product(s) in the Territory and to obtain the required regulatory approvals in relation to the Licensed Products in such Territory.

4.2. The Licensee shall conduct the following ("Diligence Requirements"):

(i) within *** from the Effective date of the Agreement conduct optimization and validation work on the Licensed Product;

(ii) within *** from the Effective date of the Agreement conduct Chemical, Manufacturing and Control development work for the Licensed Product;

(iii) within *** from the Effective date of the Agreement complete a GLP toxicology study for the Licensed Product;

(iv) within *** from the Effective date of Agreement initiate a clinical study for the Licensed Product;

(v) provide progress report within *** the end of each calendar year every twelve months.

(vi) file a New Drug Application ("NDA") or an EU equivalent within *** from the Effective date of the Agreement;

ARTICLE 5. DUE DILIGENCE

5.1. Within 30 (thirty) days after the Effective Date, Licensee shall perform due diligence research ("Due Diligence") on all data, intellectual property rights and know-how regarding the technology covered by the Licensed Patents. Licensor will facilitate all available relevant data be accessible for Licensee at the Effective Date by electronic means or other means as mutually agreed.

5.2. Any delay in the furnishing of any data shall cause the Due Diligence period as described herein to be extended with the same period as such delay as mutually agreed by both Parties. For the avoidance of doubt, Licensee shall have thirty (30) days to complete the Due Diligence as from the date on which all relevant data was made available to Licensee.

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5.3. It is expressly understood that Licensee may, at its sole discretion, terminate this Agreement within 1 (one) week after the completion of the Due Diligence ("Early Termination"), without any compensation being due to Licensor.

ARTICLE 6. ROYALTIES

6.1. Licensee will pay Licensor the Net Sales Related Royalty. The Net Sales Related Royalty will be paid, on a Licensed Product by Licensed Product and country by country basis, until the termination of this Agreement in accordance with Article 10.

Licensor will provide for the human resources, materials, facilities and equipment that are necessary for pre-clinical and clinical trials relating to the Purposes (together referred to as the "Trials Facilities"). Licensee shall be entitled to use the Trials Facilities at Licensor's standard rates (which shall be in conformity with general market rates). Such usage shall be agreed upon mutually and separate contracts shall be drafted for such purposes. If Licensee has decided not to use the Trials Facilities and in doing so has not ordered at least the equivalent of EUR *** euro's) within *** from the Effective Date or before a New Drug Application or EU Equivalent is filed (whichever is earliest), the Net Sales Related Royalty shall be increased by *** percentage points and Sublicense Royalty by *** percentage points.

6.2. Subject to the conditions set forth below, "Net Sales" shall mean:

(i) the gross amount invoiced and received by Licensee and its Affiliates for or on account of Sales of any Licensed Products, or in case of non-cash valuable considerations; the cash equivalent of such valuable considerations;

(ii) less and/or taking into account the following amounts payable by Licensee and its Affiliates in effecting such Sale:

1. amounts repaid or credited by reason of rejection or return of applicable Licensed Products;

2. reasonable and customary trade, quantity or cash rebates or discounts to the extent allowed and taken;

3. specified reasonable amounts for outbound transportation, insurance, handling and shipping; and

4. taxes, customs duties and other governmental charges levied on or measured by Sales of Licensed Products so long as Licensee's price is reduced thereby.

Specifically excluded from the definition of "Net Sales" are amounts attributable to any Sale of any Licensed Products between or among Licensee and its Affiliate, unless the transferee is the end purchaser, user or consumer of such Licensed Product.

6.3. If Licensee is required to pay Third Party Royalties, Licensee may deduct an amount equal to such Third Party Royalties from the net sales of the Licensed Products. The applicable Third Party Royalties shall be those that accrue in the same Reporting Period of the royalty reports with respect to the same transfer as the Net Sales Related Royalty and shall be calculated as provided in the third party license agreement(s), without applying any deductions or credits available to Licensee with respect to royalties paid to Licensor or to the third parties. The deductions taken for Third Party Royalties shall not reduce the net sales of the Licensed Products by more than ***. Any Third Party Royalties that are not deducted in any Reporting Period on account of this *** limitation will not be carried forward to the next Reporting Period.

6.4. Licensee will pay Licensor the Sublicense Royalty, if applicable. Such Sublicense Royalty will be paid until the termination of this Agreement in accordance with Article 10.

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6.5. After the first commercial sale of a Licensed Product, Licensee shall deliver written reports to Licensor each Reporting Period, stating in each such report the number and description of each Licensed Product sold, the Net Sales of the Licensed Products with respect thereto, the sublicense revenues received, and the calculation of Net Sales Related Royalties and Sublicense Royalties due, making reference to the specific deductions taken in accordance with the definition of Net Sales set forth in article 6.2 hereof ("Payment report").

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6.6. Licensee shall maintain full and true books of accounts and other records in sufficient detail so that the Net Sales Related Royalty and the Sublicense Royalty payable to Licensor hereunder can be properly ascertained. Such books and records shall be maintained by Licensee for a period of five (5) years from creation of individual records. Upon 10 business days' prior written knowledge, and no more frequently than once a year, Licensee shall, at the request of Licensor, permit an independent certified public accountant selected by Licensor to have access during ordinary business hours, to only such books and records as may be necessary to determine the correctness of any report or payment, including Net Sales Related Royalties and the Sublicense Royalties, made under this Agreement or to obtain information as to Net Sales Related Royalties and the Sublicense Royalties or other payments payable in case of failure to report or pay pursuant to the terms of this Agreement. Licensor shall be responsible for expenses for the independent certified public accountant initially selected by Licensor, except that Licensee shall reimburse Licensor if the independent accountant determines the amounts of Net Sales Related Royalties and the Sublicense Royalties paid by Licensee to Licensor is less than 95% of the amount of Royalties actually owed to Licensor for the period reviewed by the independent accountant. The accounting firm shall disclose to Licensor and Licensee only whether the Payment Reports are correct or not, and, if applicable the specific details concerning any discrepancies. All inspections made by Licensor hereunder shall be made no later than five (5) years after the Payment Report that is subject of the investigation was due.

6.7. For purposes of calculating the Net Sales Related Royalty and the Sublicense Royalty payment on sales of Licensed Products outside the European Union, the Net Sales of such Products shall be converted to Euros using the average closing buying rate for such currency quoted in the continental terms method of quoting exchange rates (local currency per EUR 1) by De Nederlandse Bank, on the last business day of each Reporting Period.

6.8. At its sole discretion, Licensee may elect to convert its obligation to pay Net Sales Related Royalties and Sublicense Royalties (hereinafter referred as the "Royalty-to-Pay Conversion") as laid down in this Article into one of the two lump-sum royalty options ("Conversion Lump-sum Royalty") mentioned hereinafter:

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I. before regulatory approval has been filed: EUR *** or;

II. after regulatory approval has been filed: EUR ***.

In case Licensee concludes a sublicense with a third party with regard to the Licensed Patents and the Know-How within a period of 12 (twelve) months after a conversion in accordance with this Article 6.8, and such sublicense constitutes the complete and exclusive out-licensing of the technology laid down in the Licensed Patents and the Know-How by the Licensee, the conversion will be reversed and Licensee will pay Licensor the Sublicense Royalty. Such Sublicense Royalty will be paid to Licensor as from the moment Licensee concludes a sublicense. Furthermore, the Net Sales Related Royalties are retroactively due from the notice of Royalty-to-Pay Conversion as mentioned in this Article 6.8. For the avoidance of doubt, out-licensing as used in this provision shall mean a deal in which a sublicense is concluded for the Licensed Patents and Know-How which sublicense entails that Licensee will cease its activities in the Territory under the Licensed Patents and the Know-How. In case Licensee concludes a new sublicense with a third party, this will be in accordance with this Article 6.8.

6.9 In case Licensee elected the Royalty-to-Pay Conversion, it shall inform Licensor thereof in writing. Within 30 (thirty) days after the receiving such written notice, Licensor shall send Licensee an invoice for the corresponding Conversion Lump-sum Royalty which shall be payable within 12 (twelve) months from the date of such invoice, except when the conversion is reversed because of an out-licensing within 12 months from the conversion as described under 6.8 in which case the Lump-sum Royalty shall not become payable. During this period of 12 (twelve) months, no Net Sales Related Royalties or other royalties are due by Licensee. Subject to the provisions of this Agreement, after the payment of such Conversion Lump-sum Royalty, Licensee will have a paid-up, non-terminable license under the Licensed Patents and the Know-How.

ARTICLE 7. IMPROVEMENTS

7.1. If Licensee solely makes an Improvement as defined under Article 1, Licensee shall inform Licensor thereof. Licensee shall have the right to use such Improvement without any further compensation being due. Licensor shall be entitled to use such Improvement for academic and research purposes only.

7.2. Licensee shall own Improvements made by Licensee and shall be free to register any intellectual property rights for such Improvements and to license these Improvements to third parties.

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7.3 If Licensor makes an Improvement Licensor shall inform Licensee thereof in writing within 10 days. In the event that Licensee identifies an Improvement that was made by Licensor, Licensee shall inform Licensor thereof.

Licensor herewith grants Licensee free of charge an exclusive option to obtain a license for commercial use to the aforementioned Improvements under the same terms and conditions as set out in this Agreement ("Option") for the duration of two (2) months from the date on which a Party informs the other Party of such an Improvement ("Option Period"). If Licensee informs Licensor during the Option Period that it is not interested to discuss such a license, or not inform Licensor within the Option Period, Licensor shall be free to enter into discussions and negotiations with any third party about the grant of license right to a third party to the extent that the relevant Improvements concern new oligonucleotide based compounds that may be used in the Field but that fall outside of the claims in the Licensed Patents;

If Licensee within the Option period confirms that it wishes to effectuate the Option, Parties shall in good faith either include said Improvements in this Agreement or conclude a separate license agreement covering such Improvements under the same terms and conditions as contained in this Agreement. However, in the event that an Improvement consists of new oligonucleotide based compounds that may be used in the Field but that fall outside of the claims in the Licensed Patents, those Improvements shall not be included in this Agreement, but Parties shall always conclude a separate license agreement covering such Improvements under the same terms and conditions as contained in this Agreement.

7.4 In the event that Licensee effectuates an Option on Improvements that were the result of research not fully funded by Licensee, Licensee shall pay to Licensor the part of the project costs that were not covered by Licensee, irrespective of any potential third party payments that Licensor may have received for the performance of the relevant research. Such payment will be due within 60 days of receipt of a valid invoice from Licensor. In the event that the relevant Improvements are incorporated under this Agreement, the aforementioned payments shall be included in Licensee's investments referred to in the *** EURO amount mentioned in clause 6.1. In the event that the mentioned amount of *** EURO is exceeded by the aforementioned payments while the Net Sales Related Royalty and Sublicense Royalty were already increased due to the last sentence of 6.1, both royalty percentages will be lowered to their original amounts as per the date on which the aforementioned payments were received by Licensor (and therefore not retroactively).

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

7.5 In determining the project costs not covered by Licensee –as described in 7.4 above-, personnel costs of Licensor's employees shall be calculated the rate that Licensor usually charges to commercial third Parties.

ARTICLE 8. PATENT PROSECUTION

8.1. Licensee shall bear the direct costs of patent filing and maintenance of the Licensed Patent(s). For the avoidance of doubt; Licensor will be the assignee on any patent filings.

8.2. Licensee will be the primary responsible for the maintenance of Licensed Patent(s). For this purpose, Licensor shall instruct its patent attorneys and patent agents to send all correspondence regarding the Licensed Patent(s) with a copy to Licensee. Licensee shall provide a correct correspondence address to Licensor in writing. Notwithstanding the foregoing, the Licensee will always require approval of Licensor on the drafting, filing, prosecution, procurement and maintenance of the Licensed Patent(s), such approval not to be unreasonably withheld.

8.3. In the event that Licensee elects not to file or pursue prosecution or maintenance of one or more Licensed Patent(s) in any country: (a) Licensee shall give Licensor not less than 30 days' notice before any relevant deadline, and (b) Licensor shall have the right to file and pursue, at its own expense, prosecution, procurement and maintenance of such Licensed Patent(s), without being obliged to pay any compensation to Licensee for cost and expense associated with the filing, prosecution and maintenance of the Licensed Patents incurred prior to the abandonment the Licensed Patent(s).

8.4. From the moment that Licensee is the primary responsible, Licensee shall have the first right, but not the duty, to institute infringement actions against third parties based on any Licensed Patent(s) in the Territory, at its own costs. If Licensee does not institute an infringement proceeding against an offending third party within 90 (ninety) days of learning of such infringement, Licensor shall have the right, but not the duty, to institute such an action with respect to any infringement by such third party at its own costs.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

8.5. Neither Party may enter into any settlement, consent judgment or other voluntary final disposition of such action which adversely affects any Licensed Patent(s) without the prior written consent of the other Party, which will not be unreasonably withheld. The costs and expenses of any such action (including fees of attorneys and other professionals) shall be borne by the Party instituting the action, or, if the Parties elect to cooperate in instituting and maintaining such action, such costs and expenses shall be borne by the Parties in such proportions as they may agree in writing.

8.6. Each Party shall execute all necessary and proper documents, take such actions as shall be appropriate to allow the other Party(ies) to institute and prosecute such infringement actions and shall otherwise cooperate in the institution and prosecution of such actions (including, without limitation, consenting to being named as a nominal party thereto). Each Party prosecuting any such infringement actions shall keep the other Parties reasonably informed as to the status of such actions. Any award paid by Third Parties as a result of such an infringement action (whether by way of settlement or otherwise) shall be applied first to reimburse the Parties for all costs and expenses incurred by the Parties with respect to such action on a pro rata basis and, if after such reimbursement any funds shall remain from such award, they shall be allocated as follows: (i) if Licensee has instituted and maintained such action alone, Licensee shall be entitled to retain such remaining funds; (ii) if Licensor has instituted and maintained such action alone, Licensor shall be entitled to retain such remaining funds; or (iii) if the Parties have cooperated in instituting and maintaining such action, the Parties shall allocate such remaining funds between themselves in the same proportion as they have agreed to bear the expenses of instituting and maintaining such action.

8.7. Licensee will reimburse Licensor for the cost and expense associated with the filing, prosecution and maintenance of the Licensed Patents incurred prior to and during the License Period, within 60 days after the completion of the Due Diligence described in Article 5. However, in case of Early Termination as mentioned in Article 5.3, no reimbursement of patent filing and prosecution costs will be due.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

ARTICLE 9. INVOICES AND PAYMENTS

9.1. Upon receipt of the written report mentioned in Article 6.6, Licensor shall send Licensee a royalty invoice, payable within 30 (thirty) days after the date thereof.

9.2. All payments made by Licensee or Licensor shall be in Euro.

ARTICLE 10. LICENSE PERIOD AND TERMINATION

10.1. This Agreement is entered into for the License Period, and, unless terminated earlier as provided for in this Agreement, expires automatically at the end of the License Period.

10.2. In accordance with Article 5.3, within 1 (one) week after completion of the Due Diligence period as set out in article 5.1, Licensee shall have the right, at its sole discretion, to terminate this Agreement by notifying the Licensor in writing.

10.3. Either Party may without prejudice to its right for damages, terminate this Agreement with immediate effect by giving written notice to the other Party, if the other Party is in default of a material obligation under this Agreement and has failed to cure such default, if cure is still possible and/or required by applicable law, within 30 (thirty) days after having been notified of the default by the terminating Party. A material obligation as indicated in this sub-clause includes, without limitation, any obligation laid down in Articles 4 (Diligence Requirements), 6 (Royalties), 8 (Patent Prosecution), 9 (Invoices and Payments), 13 (Warranties) and 14 (Confidentiality).

10.4. Licensor may in any event terminate this Agreement with immediate effect by giving written notice to Licensee upon the occurrence of any of the following events:

(a) Licensee applies for an order or an order is made declaring Licensee bankrupt or granting Licensee suspension of payments, or a liquidator is appointed for Licensee; or

(b) Licensee is dissolved, liquidated or ceases to carry on all or a substantial part of its business or a decision is taken to that effect; or

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

(c) In the event Licensee fails to pay any amounts due and payable to Licensor under this Agreement, and fails to make such overdue payments within thirty (30) days after receiving written notice of such failure, Licensor may terminate this Agreement immediately upon written notice to Licensee.

10.5. Licensee may terminate this Agreement with immediate effect by giving written notice to Licensor upon the occurrence of any of the following events:

(a) Licensor applies for an order or an order is made declaring Licensor bankrupt or granting Licensor suspension of payments, or a liquidator is appointed for Licensor, or any similar event occurs with respect to Licensor or any substantial part of its assets in the jurisdiction where Licensor is established; or

(b) Licensor is dissolved, liquidated or ceases to carry on its business or a decision is taken to that effect.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

ARTICLE 11. CONSEQUENCES OF TERMINATION

11.1. If this Agreement is terminated or expires, all indebtedness of Licensee to Licensor shall become immediately due and payable on the day of termination or expiry of this Agreement.

11.2. For the avoidance of doubt, after termination or expiry of the Agreement, there will be no obligation for Licensee to conduct the Diligence Requirements as set out in Article 4 and/or to reimburse Licensors costs and expenses in relation to the Licensed Patents as set out in Article 8 and/or to pay any royalties.

ARTICLE 12. –intentionally left blank-

ARTICLE 13. WARRANTIES AND LIABILTIES

13.1. Licensor warrants and undertakes to the Licensee as follows:

(i) it has the rights to grant licenses in respect of the Licensed Patent ;

(ii) it has not done, and shall not do nor agree to do during this Agreement, any of the following things if to do so would be inconsistent with the exercise by the Licensee of the rights granted to it under this Agreement, namely: (a) grant or agree to grant any rights to any third party in the Licensed Patents in the Field in the Territory; or (b) assign, mortgage, pledge, charge, or otherwise transfer any of the Licensed Patents to any third party in the Field in the Territory or any of its rights or obligations under this Agreement; and

(iii) it is not aware of any circumstance or claim that could affect the ownership and/or validity of the Licensed Patents.

13.2. With respect to the Licensed Patent(s), Licensee does not:

a) make any representations nor extends any express or implied warranties of any kind, including merchantability, accuracy, safety, or fitness for any other purpose, either written or oral;

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

b) represent that it will not infringe any patent, copyright, trade secret, trademark or other (intellectual) property rights of third parties.

13.3. Licensee is, to the extent authorised under applicable law, liable for and agrees to indemnify and defend Licensor from any liability, damage and loss, incurred by Licensee and/or third parties, which directly or indirectly result from claims, demands, costs, damage, and loss arising from or related to any liability, damage, or judgement which may be made or instituted against Licensor arising out of the license granted hereinafter of the promotion, sales or use of any Product, provided that Licensor promptly notifies Licensee of any such claim coming to its attention and that it cooperates with Licensee in the defence of such claim;

13.4. Licensee is not obliged to indemnify and hold Licensor harmless from liability as described in section 13.3 of this Agreement, in case the liability, loss or damage is a result from:

a) the negligent failure of Licensor to comply with the conditions of this Agreement or guidelines and/or any other applicable laws to this Agreement;

b) the gross negligence or wilful malfeasance of Licensor.

13.5. To the extent permissible by law, Licensor's total liability in contract, tort, misrepresentation or otherwise arising out of or in connection with this Agreement will be limited to the total payment under this Agreement.

13.6. NEITHER PARTY NOR ITS RESPECTIVE AFFILIATES SHALL BE LIABLE FOR ANY SPECIAL, INDIRECT, EXEMPLARY, CONSEQUENTIAL OR PUNITIVE DAMAGES IN CONNECTION WITH THIS AGREEMENT, WHETHER IN CONTRACT, WARRANTY, TORT, STRICT LIABILITY OR OTHERWISE.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

ARTICLE 14. CONFIDENTIALITY

14.1. The mutual non-disclosure agreement signed between Parties effective as of 22-01-2014, attached as Annex 2, shall continue in full force and effect.

ARTICLE 15. ASSIGNMENT

15.1. Licensee has the right to assign this Agreement to an Affiliate or in connection with the transfer or sale to a third party of all or substantially all of the business of Licensee to which this Agreement relates, whether by merger, sale of stock, sale of assets or otherwise. No other assignment will be allowed without the prior written consent of the other party. Licensee shall provide prompt notice to Licensor of any assignment.

15.2. An assignment agreement shall be consistent with and subject to the terms and conditions of this Agreement and any such assignment shall oblige the assignee to comply with all the terms of this Agreement. Licensee shall promptly furnish Licensor with a fully signed photocopy of all assignment agreements.

ARTICLE 16. GENERAL

16.1. Except as hereinafter provided, no Party shall be liable for any default or delay in the performance of the terms of this Agreement where such failure is due to Force Majeure affecting that Party.

16.2. Upon the occurrence of an event constituting Force Majeure, the Party affected by this event shall take all measures which may reasonably be required to rectify the situation as quickly as possible. The Parties shall, if necessary, jointly examine the measures to be taken to limit the effect of Force Majeure.

16.3. In the event that a Party wishes to rely on a condition of Force Majeure, that Party shall notify the other Party orally as soon as reasonably possible, but in no case later than 48 (forty-eight) hours after discovery of such condition; such oral notice shall be followed by a notice by the Party claiming such condition of Force Majeure to the other Party within 5 (five) days of discovery.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

16.4. Except as otherwise provided in this Agreement, no amendment to this Agreement shall have any force or effect unless it is in writing and signed by authorised representatives of both Parties.

16.5. This Agreement shall be binding upon and inure to the benefit of the Parties hereto and their respective successors, estates and, in the event of a permitted assignment or transfer, assignees or transferees.

16.6. No failure or delay on the part of either Party to exercise any right or remedy under this Agreement shall be construed or operate as a waiver thereof, nor shall any single or partial exercise of any right or remedy preclude the further exercise of such right or remedy.

16.7. If any provision or part of this Agreement is held to be invalid, amendments to this Agreement may be made by the addition or deletion of wording as appropriate to remove the invalid part or provision but otherwise retain the provision and the other provisions of this Agreement to the maximum extent permissible under applicable law.

16.8. This Agreement, including its Annexes sets out the entire agreement between the Parties relating to its subject matter and supersedes all prior oral or written agreements, arrangements, or understandings between them relating to such subject matter.

16.9. Except as specifically provided otherwise herein, each Party shall bear its own costs in connection with the preparation, negotiation, signing or performance of this Agreement.

ARTICLE 17. NOTICES

17.1. Unless otherwise provided herein, any royalty reports, notice or other communications under or in connection with this Agreement shall be in writing and sent by e-mail, by courier, or by registered mail and shall be effective when received, and in any event no later than when sent:

(a) by e-mail **2 (two)** business hours after receipt. “Business hour” shall mean any time between 09.00 and 18.00 hours on a business day in the country of the addressee.

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

(b) by courier service **3 (three)** working days after dispatch,

(c) by registered mail **3 (three)** working days after dispatch.

17.2. For the purposes hereof, the addresses of the Parties shall be as specified below:

If to Licensee:

Licensee	**ProQR Therapeutics B.V.**
Address	**Darwinweg 24**
	2333 CR Leiden
	The Netherlands
E-mail	***
Attn	**Daniel A. de Boer**
With copy to	**Bart Klein**
Address	**Darwinweg 24**
	2333 CR Leiden
	The Netherlands
E-mail	***
Attn	**[ ]**

If to Licensor:

Licensor:	**Radboud University Medical Center**
Address	**Geert Grooteplein 10**
	P.O. BOX 9101
	6500 HB Nijmegen
	The Netherlands
E-mail	**[ ]**
Attn	**[ ]**

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

With copy to
E-mail ***

or at such other address as the Party to be given notice may have notified to the other from time to time in accordance with this clause for that purpose.

17.3. The provisions of this clause shall not apply in relation to the servicing of documents for the purpose of litigation.

ARTICLE 18. GOVERNING LAW

18.1. The validity, construction, and performance of this Agreement shall be governed by the laws of the Netherlands.

18.2. Any dispute, controversy or claim arising under, out of or relating to this Agreement and any subsequent amendments of this Agreement, shall be submitted to the exclusive jurisdiction of the competent court of Amsterdam, the Netherlands.

This Agreement has been signed in two counterparts, each of equal tenor and validity

(Signatures on next page)

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

For and on behalf of

Stichting Katholieke Universiteit,

Radboud University Medical Center

By: Prof. Dr. H.G. Brunner
Title: Head of the Human Genetics Dept.
Date:

By: Dr. D. Masman
Title: Director of Valorisation/Tech Transfer
Date:

For and on behalf of

ProQR Therapeutics B.V.

By: Daniel de Boer
Title: Chief Executive Officer
Date:

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

ANNEX 1

PCT (NL) application No. 2012/050275 (published as WO2013036105)

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

ANNEX 2 CDA

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

DECLARATION FOR REGISTRATION OF LICENSE

THE UNDERSIGNED

1. Stichting Katholieke Universiteit, doing business as the Radboud University Medical Center, a foundation organised under the laws of the Netherlands, established at Geert Grooteplein Noord 9, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands, registered at the Dutch Chamber of Commerce under number 41055629; (hereinafter referred to as "Licensor");

AND

2. ProQR Therapeutics B.V., a company organised under the laws of The Netherlands, whose corporate seat is at Utrecht and whose offices are at Darwinweg 24, 2333 CR Leiden, registered at the Dutch Chamber of Commerce under number 54600790, duly represented by its CEO D. A. de Boer, hereinafter referred to as the "Licensee";

NOW HEREBY DECLARE AS FOLLOWS:

Pursuant to a license agreement between Licensor and Licensee, Licensor has granted Licensee a license to use patents and patent application listed in Annex 1, which license Licensee has accepted.

Licensor agrees to the registration of Licensee in the register as its licensee for the said patents and patent applications effective from the date below.

On behalf of Licensor	**On behalf of Licensee**
name:	name:
title:	title:
date:	date:

PORTIONS OF THIS EXHIBIT WERE OMITTED AND HAVE BEEN FILED SEPARATELY WITH THE SECRETARY OF THE COMMISSION PURSUANT TO AN APPLICATION FOR CONFIDENTIAL TREATMENT UNDER RULE 406 OF THE SECURITIES ACT; * DENOTES OMISSIONS**

Exhibit 8.1

SUBSIDIARIES OF PROQR THERAPEUTICS N.V.

The following is a list of subsidiaries of the Company (and jurisdiction of incorporation) as of December 31, 2016.

- ProQR Therapeutics Holding B.V. (the Netherlands);
- ProQR Therapeutics I B.V. (the Netherlands);
- ProQR Therapeutics II B.V. (the Netherlands);
- ProQR Therapeutics III B.V. (the Netherlands);
- ProQR Therapeutics IV B.V. (the Netherlands);
- ProQR Therapeutics VI B.V. (the Netherlands);
- ProQR Therapeutics VII B.V. (the Netherlands);
- ProQR Therapeutics VIII B.V. (the Netherlands);
- ProQR Therapeutics IX B.V. (the Netherlands);
- ProQR Therapeutics I Inc. (Delaware, United States).

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, 2017

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, 2017

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, 2016, 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, 2017

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. 207245) of our report dated March 31, 2017 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, 2016.

/s/Deloitte Accountants B.V.

Amsterdam, the Netherlands
March 31, 2017