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, 2017

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)

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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: 31,921,865

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 ☒ Emerging growth company

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards† provided pursuant to section 13(a) of the Exchange Act.

†The term "new or revised financial accounting standard" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012.

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, 2017 of ProQR Therapeutics N.V. (the "2017 Form 20-F"). Unless the context specifically indicates otherwise, references in this 2017 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, 2017 and 2016, and for the years ended December 31, 2017, December 31, 2016 and December 31, 2015, included in the 2017 Form 20-F have been prepared in accordance with International Financial Reporting Standards (IFRS) as issued by the International Accounting Standards Board (IASB).

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" and "Axiomer" are our trademarks. 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 eluforsen (formerly known as QR-010), QR-110, QR-313, QR-421a or any other pipeline program, to be materially different from any future results, performance or achievements, including in relation to the clinical development of eluforsen, QR-110, QR-313, QR-421a 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 2013 through 2017.

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, 2017	Year Ended December 31, 2016	Year Ended December 31, 2015	Year Ended December 31, 2014	Year Ended December 31, 2013
	(€ in thousands, except for per share data)				
Statement of comprehensive loss data:					
Other income	1,495	1,828	3,235	313	116
Research and development costs	(31,153)	(31,923)	(23,401)	(10,267)	(2,569)
General and administrative costs	(10,840)	(9,478)	(6,837)	(6,507)	(786)
Operating result	**(40,498)**	**(39,573)**	**(27,003)**	**(16,461)**	**(3,239)**
Finance income and expense	(3,175)	470	6,171	4,334	(14)
Corporate income taxes	(2)	—	—	—	—
Result for the year	**(43,675)**	**(39,103)**	**(20,832)**	**(12,127)**	**(3,253)**
Other comprehensive income	151	(16)	1	—	—
Total comprehensive loss (attributable to equity holders of the Company)	**(43,524)**	**(39,119)**	**(20,831)**	**(12,127)**	**(3,253)**
Share information					
Weighted average number of shares outstanding	25,374,807	23,346,507	23,343,262	11,082,801	5,517,688
Earnings per share for result attributable to the equity holders of the Company (expressed in Euro per share) Basic and diluted loss per share	€ (1.72)	€ (1.67)	€ (0.89)	€ (1.09)	€ (0.59)

	As at December 31,				
	2017	2016	2015	2014	2013
	(€ in thousands)				
Statement of financial position data:					
Cash and cash equivalents	48,099	59,200	94,865	112,736	4,129
Total assets	53,103	65,543	100,109	115,247	4,504
Total liabilities	13,778	12,407	10,310	5,843	4,593
Total shareholders' equity	39,363	53,136	89,799	109,404	(89)

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 $ 1.1993 to € 1.00, the official exchange rate quoted by the European Central Bank at the close of business on December 31, 2017. As at March 9, 2018, the official exchange rate of Euro to U.S. dollars was $ 1.2291 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,				
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
2017	1.1993	1.1297	1.0385	1.2060
Month ended				
September 30, 2017	1.1806	1.1915	1.1741	1.2060
October 31, 2017	1.1638	1.1756	1.1605	1.1856
November 30, 2017	1.1849	1.1738	1.1562	1.1952
December 31, 2017	1.1993	1.1836	1.1736	1.1993
January 31, 2018	1.2457	1.2200	1.1932	1.2457
February 28, 2018	1.2214	1.2348	1.2214	1.2493

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 product candidates in cystic fibrosis (CF), eluforsen, Leber's congenital amaurosis (LCA), QR-110, epidermolysis bullosa (EB), QR-313 and Usher syndrome, QR-421a. We have had significant operating losses since our inception. Our net losses for the years

ended December 31, 2015, December 31, 2016 and December 31, 2017 were € 20,832,000, € 39,103,000 and € 43,675,000 respectively. At December 31, 2017, we had an accumulated deficit of € 119,370,000. 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 eluforsen, QR-110, QR-313, QR-421a 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 eluforsen, if ever, will trigger a milestone payment to Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, of approximately $ 16 million pursuant to our agreement with CFFT, and we may not have sufficient funds to support this payment obligation. Commercialization of QR-421a will trigger payments of up to $ 37.5 million pursuant to our agreement with Foundation Fighting Blindness, or FFB. 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 these transactions.

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, 2017, we had € 48,099,000 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 into the second half of 2019. 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, eluforsen, has only in 2017 completed its second 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, or involve delays to the clinical trials. 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 trials 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 trials and pre-clinical testing of our 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 eluforsen, QR-110, QR-313, QR-411 or QR-421a, or obtain such status for 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. 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 several of our product candidates 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 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 eluforsen, QR-110, QR-313, QR-411 and QR-421a, 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 eluforsen for CF and QR-110 for LCA. We intend to seek fast track designation for QR-313, QR-411 and QR-421a, 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 eluforsen 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. 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, and to patent rights owned by Inserm Transfert, or Inserm, for the commercial exploitation of antisense oligonucleotides that cause exon skipping in *CEP290* pre-mRNA. For our Usher program we have a world-wide exclusive sublicensable and royalty-bearing license to patent rights owned by Radboud, for the commercial exploitation of antisense oligonucleotides that cause exon skipping in *USH2A* pre-mRNA.

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, Radboud and Inserm, as well as our other licensors, may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, MGH, Radboud and Inserm, 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 for a significant amount of time. 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 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. 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. An overview of potential competitors is included in Item 4.B: “Business overview - Competition”.

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.

Even if any of our product candidates is 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. 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, 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.

In addition, we have estimated the size of patient populations and market potential for certain of the indications that our product candidates are intended to target. While we have based our estimates on industry and market data that we obtained from sources, including scientific journals, that we believe to be reliable, actual potential may differ from these estimates.

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 eluforsen, if ever, will trigger a milestone payment to CFFT of approximately $ 16 million pursuant to our agreement with CFFT. Commercialization of QR-421a will trigger payments of up to $ 37.5 million pursuant to our agreement with FFB. We may not have sufficient funds to support our milestone payment obligations to CFFT and FFB, 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. In December 2017, President Trump signed into law the Tax Cuts and Jobs Act of 2017, which includes a repeal of the individual mandate under the Affordable Care Act. Additionally, in October 2017, President Trump signed an Executive Order directing federal agencies to review regulations applicable to association health plans and short-term health insurance, and announced that the administration would halt federal subsidies to insurance plans under the Affordable Care Act. There is significant uncertainty whether any other 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.

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.

We are increasingly dependent on information technology systems, and our systems and infrastructure face certain risks, including from cyber security breaches and data leakage.

We increasingly rely upon technology systems and infrastructure, including support provided by our partners and third parties, to support our business. For example, we routinely rely on our technology systems and infrastructure to aid us in the collection, use, storage and transfer, disclosure and other processing of voluminous amounts of data (including confidential, business, personal and other sensitive information). We also rely on systems for manufacturing, regulatory compliance and various other matters.

The increasing use and evolution of technology, including cloud-based computing, and reliance on third parties creates additional opportunities for the unintentional, intentional and/or unauthorized exposure, dissemination and/or destruction of confidential information stored in our technology systems, infrastructure and products. Our computer systems, servers and other technology systems (and those of third parties that we use) are vulnerable to breakdown, interruption, cyber and other security attacks, system malfunction, unauthorized access and other events. Security threats, including cyber and other attacks are becoming increasingly sophisticated, frequent, and adaptive. Any such vulnerability could compromise our technology systems and infrastructure and could expose personal and/or proprietary information (including sensitive personal information) to unauthorized third parties and/or cause permanent loss of such data. While

we have invested in the protection of data and information technology, there can be no assurance that our efforts will prevent breakdowns, breaches in our systems or other incidents or ensure compliance with all applicable security and privacy laws, regulations and standards. Such breakdowns can lead to regulatory fines and penalties, business disruption, reputational harm, financial loss as well as other damages. We could also suffer strained relationships, increased costs (for security measures, remediation or otherwise), litigation (including class actions and stockholder derivative actions) or other negative consequences (including a decline in stock price) from breaches, cyber and other security attacks, industrial espionage, ransomware, email or phishing scams, malware or other cyber incidents, which may compromise our system infrastructure or lead to data leakage, either internally or at our third-party providers or other business partners. While we have invested in the protection of data and information technology and in related training, there can be no assurance that our efforts will prevent significant breakdowns, attacks, breaches in our systems or other cyber incidents or ensure compliance with all applicable security and privacy laws, regulations and standards, including with respect to third-party service providers that utilize sensitive personal information, including protected health information on our behalf.

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, 2017, we had € 48,099,000 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 it is our policy to match the currency of our cash and cash equivalents with expected cash out flows as much as practically feasible. 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, 2017, we had a total of approximately € 123.9 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.

The effect of comprehensive U.S. tax reform legislation on ProQR and its affiliates, whether adverse or favorable, is uncertain.

On December 22, 2017, President Trump signed into law H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018" (informally titled the "Tax Cuts and Jobs Act"). Among a number of significant changes to the U.S. federal income tax rules, the Tax Cuts and Jobs Act reduces the marginal U.S. corporate income tax rate from 35% to 21%, limits the deduction for net interest expense, shifts the United States toward a more territorial tax system, and imposes new taxes to combat erosion of the U.S. federal income tax base. The effect of the Tax Cuts and Jobs Act on ProQR and its affiliates, whether adverse or favorable, is uncertain, and may not become evident for some period of time. You are urged to consult your tax adviser regarding the implications of the Tax Cuts and Jobs Act for an investment in ProQR.

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 $2.80 per share at the close of the trading on December 12, 2017. 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, 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 and, in case we become a domestic filer, 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.

Our management board will be required to assess the effectiveness of our internal controls and procedures annually and, in case we become a domestic filer, we will be required to disclose changes to these controls on a quarterly basis. 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 prior offerings. Based on the average value of our gross assets, we believe that we were not a PFIC for the 2017 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 Leber's congenital amaurosis 10, Usher syndrome type 2A, dystrophic epidermolysis bullosa and cystic fibrosis. 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, the late Henri Termeer and Dinko Valerio. Mr. de Boer is a passionate and driven entrepreneur and an advocate for patients with severe genetic disorders. He has assembled an experienced team of successful biotech executives as co-founders, management team members and early investors. The team has extensive experience in the discovery and development of products in multiple therapeutic areas. As of December 31, 2017, we had raised approximately €160 million in gross proceeds from our public offerings of shares on the NASDAQ Global Market and private placements of equity securities. In addition, we have received grants, loans and other funding from patient organizations and government institutions supporting our programs, including from Cystic Fibrosis Foundation Therapeutics, Inc., a subsidiary of the Cystic Fibrosis Foundation, Foundation Fighting Blindness and the European Union under their Horizon 2020 research and innovation programme, grant agreement No. 633545. ProQR headquarters are located in Leiden, the Netherlands.

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 engaged in the discovery and development of RNA-based therapeutics for the treatment of severe genetic orphan disorders. Utilizing our RNA platform, we are building a pipeline of therapeutics for patients in need. Our drug development programs are based on single-stranded RNA oligonucleotides that are chemically modified to enhance stability and cellular uptake, and aimed to restore protein function through targeting the RNA. While all our compounds are one therapeutic modality, a variety of mechanisms of actions may be used depending on the mutation that is targeted. We believe that this targeted approach offers several advantages compared to other therapeutic approaches in the treatment of the rare genetic diseases we target.

Our current pipeline consists of programs in ophthalmology, dermatology and cystic fibrosis. For ophthalmology, we have a deep and broad pipeline that includes: QR-110 for Leber's congenital amaurosis 10, or LCA 10, caused by the

p.Cys998X mutation in the *CEP290* gene, which we are currently studying in a Phase 1/2 clinical trial that is expected to have six-month treatment data in 2018 and twelve-month treatment data in 2019; QR-421a for the ophthalmic manifestations of Usher syndrome 2A due to exon 13 mutations in the *USH2A* gene and QR-411 for the ophthalmic manifestations of Usher syndrome 2A due to the PE40 mutation in the *USH2A* gene, which are both in pre-clinical development and with QR-421a advancing towards the clinic at the end of 2018; QRX-1011 for Stargardt's disease due to an exon 39 splicing mutation in the *ABCA4* gene in discovery stage; and QRX-504 in late discovery stage for Fuchs' endothelial corneal dystrophy type 3, or FECD3, caused by a repeat expansion mutation in the *TCF4* gene. For cystic fibrosis, a severe genetic disease, we are developing eluforsen (formerly QR-010) for the F508del mutation in *CFTR*, which has completed two clinical trials in CF patients with positive data. A Phase 2 study for eluforsen is currently being designed and is planned to commence in 2018 subject to a partnership. In addition to our eluforsen program, we also have a discovery pipeline for other genetic mutations causing CF. In dermatology, QR-313 targets a specific set of mutations located in exon 73 of the *COL7A1* gene that leads to dystrophic epidermolysis bullosa, or DEB, a severe genetic blistering skin disease. IND-enabling studies of QR-313 have been completed and we plan to start a Phase 1/2 study in 2018. Interim data from this trial will be available in 2018 and final data in 2019.

Beyond that, we have discovered and developed a novel proprietary RNA editing platform technology called Axiomer. Axiomer's editing oligonucleotides, or EONs, are designed to recruit endogenous Adenosine Deaminases Acting on RNA, or ADAR, enzymes to make single nucleotide changes in the RNA in a highly specific and targeted manner at the desired location. We believe our Axiomer platform may be applicable to more than 20,000 disease-causing mutations. We completed optimization of proof-of-concept *in vitro* and *in vivo* in 2017. In January 2018, we announced a research collaboration with Galapagos N.V., where we are applying this novel technology to target certain fibrosis targets identified by Galapagos. We plan to build out our Axiomer platform in select therapeutic areas and continue to validate and create value for this technology through licensing, partnering and other strategic relationships.

We have also discovered and developed together with the Leiden University Medical Center, a program for hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D). HCHWA-D, or Katwijks disease, a genetically defined subpopulation of cerebral amyloid angiopathy, or CAA. In 2017, we spun out this program into Amylon Therapeutics B.V., in which we maintain a majority ownership.

We are also developing QRX-704, an oligonucleotide-based approach for Huntington's disease (HD), an inherited progressive neurodegenerative disease caused by a mutation in the *HTT* gene, and one of the most common genetic disorders. Patients with HD have shortened life expectancy and there is currently no disease-modifying treatment available.

We continue to assess our development and commercialization plans for our product candidates and intend to evaluate opportunities for beneficial collaborations or partnerships for these programs. In addition, using our discovery engine that is designed to generate a deep and broad pipeline of product candidates, we seek to enter into strategic partnerships for programs that we believe will benefit from such a partnership, and advance other selected programs independently to commercialization.

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 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.

We believe our extensive pipeline, strong team and excellent partners 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.

Research and development pipeline

QR-110 and Leber's Congenital Amaurosis 10 (LCA 10)

Leber's Congenital Amaurosis 10 (LCA 10) is the most common genetic cause of blindness in childhood. LCA is caused by a genetic defect in 20 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* (encoding centrosomal protein of 290 kDa) that is associated with LCA 10. The most common mutation is the p.Cys998X (also known as c.2991+1655A>G) in the *CEP290* gene. Although prevalence 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 for LCA 10, QR-110, is a first-in-class oligonucleotide designed to treat the disease by repairing the underlying cause in the mRNA, which results in the production of the normal, or 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 expression, which could lead to the production of normal or wild type CEP290 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 supports 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 affected 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.

We are currently conducting an open-label Phase 1/2 clinical trial of QR-110 in adult and pediatric LCA 10 patients with one or two copies of the *CEP290* p.Cys998X mutation. Our ongoing Phase 1/2 safety and tolerability study will enroll six pediatric patients (age 6 - 17) and six adults (≥ 18 years). Patient dosing commenced in November 2017. Patients will receive one loading dose and three maintenance doses over the period of 12 months in one eye. Three different dosing regimens will be tested: a low dose group (160 µg loading dose / 80 µg maintenance dose), a mid dose group (320 µg loading dose / 160 µg maintenance dose) and a high dose group (500 µg loading dose / 270 µg maintenance dose). The study is being conducted at three sites in the U.S. and Belgium and being overseen by a Data Monitoring Committee. We expect to obtain six-month treatment data from this study in 2018 and full twelve-month data in 2019. There is recent precedent for an accelerated development path in another LCA subtype, and we believe this accelerated development pathway can potentially be applied to QR-110.

QR-110 has been granted orphan drug designation by the FDA and European Commission and received fast track designation by the FDA for the treatment of LCA 10.

QR-421a and QR-411 for Usher syndrome type 2A.

Usher syndrome is the leading cause of combined hearing loss and blindness. Patients with Usher syndrome 2A generally progress to a stage in which they have very limited central and peripheral vision and moderate to severe deafness. To date, there are no therapies approved or product candidates in clinical development that treat the vision loss associated with Usher syndrome 2A. Usher syndrome 2A is one of the most common forms of Usher syndrome and is caused by mutations in the *USH2A* gene. We are developing QR-421a for the ophthalmic manifestation of Usher syndrome 2A due to exon 13 mutations and QR-411 for the ophthalmic manifestations of Usher syndrome 2A due to the PE40 mutation. Mutations in exon 13 of the *USH2A* gene affect approximately 16,000 patients in the United States, European Union, Canada and Australia. Mutations in PE40 of the *USH2A* gene affect approximately 1,000 patients in the United States, European Union, Canada and Australia. Both product candidates are single-stranded oligonucleotides intended to be administered by intravitreal injections and that aim to restore a functional usherin protein to restore vision.

Pre-clinical development of QR-421a has begun and we plan to advance this program towards a Phase 1/2 safety and efficacy clinical trial at the end of 2018. The planned trial consists of a single-dose arm and a six-month adaptive multiple dose arm. We expect to receive top-line data from the single-dose arm in the first half of 2019 and from the adaptive multiple-dose arm later in 2019.

On February 9, 2018, we entered into a partnership agreement with Foundation Fighting Blindness (FFB), under which FFB has agreed to provide funding of $7.5 million to advance our QR-421a into the clinic and will receive future milestone payments.

QR-421a and QR-411 have both been granted orphan drug designation by the FDA and European Commission for Usher sydrome type 2.

We are also developing QRX-1011 for Stargards disease due to an exon 39 splicing mutation in *ABCA4* and QRX-504 for Fuchs' endothelial corneal dystrophy 3. Both programs are in the optimization phase, which is the last stage in discovery. Once optimized, we intend to advance these molecules into pre-clinical development.

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 wounds that result from minimal friction. 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 this disease is also associated with significant morbidity. There is currently no

treatment available for DEB. Intensive 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 the formation of anchoring fibrils that link the epidermis to the dermis.

We are developing a first-in-class single-stranded oligonucleotide, QR-313, for patients with DEB caused by mutations in a specific part of the *COL7A1* gene called exon 73. There are multiple mutations associated with DEB, several of which lie within exon 73. QR-313 is designed to exclude exon 73 from the *COL7A1* mRNA. Skipping of exon 73 leads to an mRNA that lacks the mutation causing the disease. This mRNA is translated into a truncated but functional C7 protein that is able to form anchoring fibrils and improve the strength of the skin.

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 C7 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.

We are planning to commence our first in human study of QR-313 in DEB exon 73 patients in 2018, which we refer to as WINGS (A First in Human, Double-Blind, Randomized, Intra-Subject Placebo-Controlled, Multiple Dose Study of QR-313 Evaluating Safety, Proof of Mechanism, Preliminary Efficacy and Systemic Exposure in Subjects With Recessive Dystrophic Epidermolysis Bullosa (RDEB) due to Mutation(s) in Exon 73 of the *COL7A1* Gene). We plan to conduct the WINGS study as a Phase 1/2 safety and efficacy clinical trial in two parts, first enrolling eight RDEB patients with an exon 73 mutation, and after interim analyses expect to add another cohort of DEB patients. The study evaluaties safety, tolerability and systemic passage of QR-313. The clinical trial is expected to be double blinded intra-patient controlled, single or dual-wound treatment for 4 weeks, with a follow-up period of 8 weeks. We expect to receive interim data from the first part of the trial in 2018 and full results in 2019. Beyond QR-313, we have a pipeline of discovery-stage programs for other mutations that cause DEB, including QRX-323 and QRX-333.

QR-313 has been granted orphan drug designation in the United States and the European Union for the treatment of patients with DEB with exon 73 mutations.

Eluforsen and Cystic Fibrosis (CF)

Cystic fibrosis 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 65,000 CF patients, representing 85% of the 77,000 CF patients in the Western world. In CF patients, 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 for CF, eluforsen, is a first-in-class RNA-based oligonucleotide 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. Eluforsen 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 eluforsen 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 eluforsen in 2015. In 2016, we presented positive results from PQ-010-002, a proof-of-concept trial demonstrating that eluforsen 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, eluforsen 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. Eluforsen was observed to be well-tolerated in all subjects.

The 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 was conducted in 26 sites in North America and Europe. The primary endpoint of the trial was to evaluate the safety, tolerability and pharmacokinetics, of single and multiple ascending doses of inhaled eluforsen in CF patients carrying two copies (homozygotes) of the F508del mutation. This trial also assessed a number of exploratory efficacy endpoints, although the trial was not powered for statistical significance on these endpoints. The results of the single-dose cohorts were reported in 2016 and all doses were safe and well-tolerated. In September 2017, we reported the preliminary results of the multiple-dose cohorts in which 36 subjects were enrolled. Eluforsen was observed to be safe and well-tolerated across all doses with no serious adverse events related to treatment. A clinically meaningful improvement of CF respiratory symptoms, as measured by CFQ-R RSS (Cystic Fibrosis Questionnaire-Revised Respiratory Symptom Score) was observed in 3 out of 4 multiple dose groups with a mean improvement of 13.0 to 19.2 points compared to placebo. The magnitude of the benefit observed in CFQ-R RSS for these dose groups exceeded the established minimal clinically important difference of 4.0 points. In addition, a supportive trend of improved lung function was observed up to 4.0% mean absolute change in ppFEV1 compared to placebo. There were no changes in weight gain and sweat chloride. A Phase 2 trial is currently under design and is planned to commence in 2018 subject to a partnership.

Eluforsen has been granted orphan drug designation in the United States and the European Union and has received Fast Track designation from the FDA for the treatment of patients with CF due to the F508del mutation.

Besides our program for CF caused by the F508del mutation, we are working on other *CFTR* mutations that could be treated using our RNA technologies. We could potentially target up to 12,000 patients, representing an estimated 15% of CF patients in the Western world, with these programs.

Axiomer RNA Editing Technology Platform

As a result of several years research conducted at ProQR in collaboration with academic partners, ProQR has invented and patented a novel RNA editing platform technology called Axiomer. Axiomer is a platform that can modify individual RNA bases and therefore target certain genetic mutations that cause disease. This technology uses the well-established therapeutic modality of single stranded RNA oligonucleotides, designed in a way to recruit an endogenous enzymatic complex called ADAR, and guided to make a change to the RNA exactly where we want it. We call the molecules Editing OligoNucleotides, or EONs. The Axiomer EONs can specifically target G-to-A mutations, and can therefore potentially treat over 20.00 disease causing G-to-A mutations that are described in literature.

Recruitment of endogenous RNA editing enzymes by oligonucleotides represents a significant therapeutic opportunity for a new type of drugs that can treat genetic disorders by reversing the underlying mutations. Deamination of adenosines into inosines (A-to-I editing) is the most common type of single-nucleotide post-transcriptional editing, with a predictable change in the base-pairing specificity: As inosine base-pairs with cytosines, the editing effectively results in an A-to-G conversion, which in turn can affect RNA processing (e.g. splicing or RNA stability) or the codon identity during translation. The reaction is catalyzed by the ADAR enzymes (Adenosine deaminases acting on RNA), and takes place on different substrates, including (pre-) mRNAs, miRNAs and lncRNAs, and in a range of disease-relevant tissues. We have invented and developed an approach where the endogenous ADAR can be recruited by using an oligonucleotide only, without the need for overexpression of ADAR (fusion) proteins or long guide RNAs. The oligonucleotides, referred to as Editing Oligonucleotides (EONs), are designed so as to allow the editing reaction to be specific for the target adenosine and to bestow general drug-like properties, without interfering with ADAR binding and activity. The design includes structural features and chemical modifications of the oligonucleotide backbone, to provide for stability and cellular uptake, and enable the EONs to recruit the endogenous ADARs and direct them to specifically edit one selected adenosine, while suppressing the editing of other, off-target adenosines. We have named this proprietary innovative technology Axiomer RNA editing technology.

We have provided proof of concept for our Axiomer technology in a mouse model of the Hurler syndrome, a lysosomal storage disorder caused by inactivation of the alpha-L-iduronidase enzyme. The underlying G-to-A mutation is corrected by EON-directed A-to-I editing in the Idua transcript, resulting in restoration of protein translation and enzymatic activity. *In vitro* work with additional models indicates that the EONs are generally applicable for the correction of mRNA G-to-A mutations, over 20,000 of which are known to cause monogenetic disorders. We are currently exploring the use of our Axiomer RNA Editing technology to continue to develop therapies for genetic disorders that have no or less effective or less safe treatment options in select therapeutic areas. In addition to initiating in-house programs, we plan to continue to validate and create value for our Axiomer technology by entering into licensing and collaboration agreements in select therapeutic areas. In January 2018, we announced a research collaboration agreement with Galapagos, N.V. where we are applying our novel Axiomer technology to fibrosis targets identified by Galapagos. We are also using our Axiomer technology to target several premature stop codon mutations in CF.

Discovery Programs

On our mission to make a positive impact to the lives of patients that suffer from rare diseases, we continuously look for ways to apply our science and know-how to expand our reach. As a part of that we are building out our platform technologies to new diseases and therapeutic areas. As our technologies can potentially treat thousands of disease causing mutations we have to prioritize where to apply our science next. We therefore have a rigorous evaluation process in identifying programs for our pipeline that includes establishing genetic causality, ability to deliver drug to the target organ, intellectual property protection, strong proof of concept, and a high unmet need. Our early stage programs are in various stages of discovery and target different severe genetic disorders where we believe our technologies have the potential to deliver therapeutic benefits to affected patients.

QRX-704 for Huntington's Disease

QRX-704 is a discovery stage oligonucleotide approach for the treatment of Huntington's disease (HD). 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. Patients 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 *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 designed to modify the *HTT* mRNA to prevent the formation of the toxic fragments, while the huntingtin protein remains functional.

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 Leber's congenital amaurosis 10, Usher syndrome 2A, dystrophic epidermolysis bullosa and cystic fibrosis. 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.

- ***Rapidly advance our ophthalmology franchise, including QR-110 for the treatment of LCA.*** We recognize the great opportunity for oligonucleotides in the ophthalmology space and therefore have established an ophthalmology franchise with programs for LCA 10, Usher syndrome 2A, Fuchs' endothelial corneal dystrophy 3 and Stargardt's disease. We are currently conducting a Phase 1/2 clinical trial of our lead product candidate, QR-110, in adults and children with LCA 10, the leading genetic cause of blindness in childhood. Patient dosing commenced in late 2017 and we expect to obtain six-month treatment data in 2018 and full twelve-month data in 2019.

- ***Extensively broaden our ophthalmology portfolio by advancing QR-421a and QR-411 for Usher syndrome 2A into clinical development.*** For Usher syndrome 2A, a progressive disease leading to hearing loss and blindness, we are developing QR-421a for the ophthalmic manifestation of Usher syndrome 2A due to exon 13 mutations, and QR-411, also for Usher syndrome 2A due to the PE40 mutation. In 2018, we plan to advance QR-421a towards a Phase 1/2 clinical trial with results expected in 2019. Other programs in our ophthalmology franchise include QRX-1011 for Stargardt's disease and QRX-504 for Fuchs' endothelial corneal dystrophy 3, both in the optimization phase, considered the last stage of discovery. Once optimized, we intend to advance these molecules into pre-clinical development.

- ***Initiate the first in human clinical trial for QR-313, our lead dermatology candidate, for the treatment of DEB.*** Our QR-313 candidate is designed to address the underlying cause of DEB, a severe genetic blistering skin disease due to mutations in exon 73 of the *COL7A1* gene. A Phase 1/2 study for QR-313 is planned to start in 2018 and we expect to obtain interim data in 2018 and full data in 2019. Beyond QR-313, we have a pipeline of discovery-stage programs for other mutations that cause DEB, including QRX-323 and QRX-333.

- ***Expand our Axiomer RNA-editing platform into select therapeutic areas and capture value through product and business development efforts.*** Our novel and proprietary RNA editing platform technology, called Axiomer, is a new way to use oligonucleotides to edit single nucleotides in the RNA. We believe our Axiomer technology may be applicable to more than 20,000 disease-causing mutations. In 2018 and beyond, we plan to build out Axiomer in select therapeutic areas and continue to validate and create value for the platform through pursuing licensing, partnering and other strategic relationships.

- ***Seek a partner to develop and commercialize eluforsen for the treatment of CF.*** Our lead product candidate for CF, eluforsen, has generated compelling data in pre-clinical and two global clinical studies in CF patients. Results from our Phase 1b study announced in 2017 found eluforsen to be safe and well-tolerated and demonstrated encouraging efficacy responses. The positive data support the potential of eluforsen as a disease-modifying therapy for CF patients with two copies of the F508del mutation. We intend to pursue a strategic partnership for the development and commercialization of eluforsen and start a planned Phase 2 trial in 2018. We are also studying applications of RNA technologies for other CF mutations which currently have no available therapies.

- ***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.

Patient Centric Approach

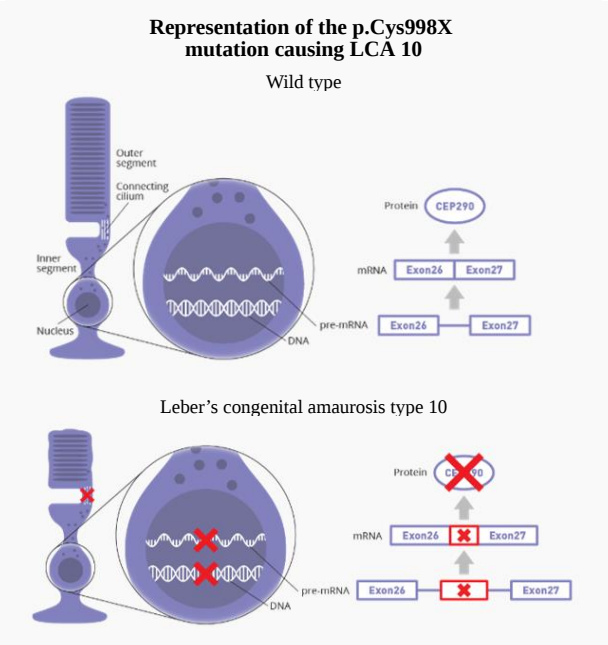
ProQR aims to develop best-in-class therapies as well as to improve patient care through awareness, education, and advancing the understanding of conditions that we target. In order to achieve this goal, ProQR strives to integrate the patient voice into our decision-making throughout the drug development 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.

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 LCA 10 include loss of vision, involuntary eye movement or nystagmus, abnormalities of pupil reactions and no detectable photoreceptor electrical signals on electroretinography (ERG).



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.

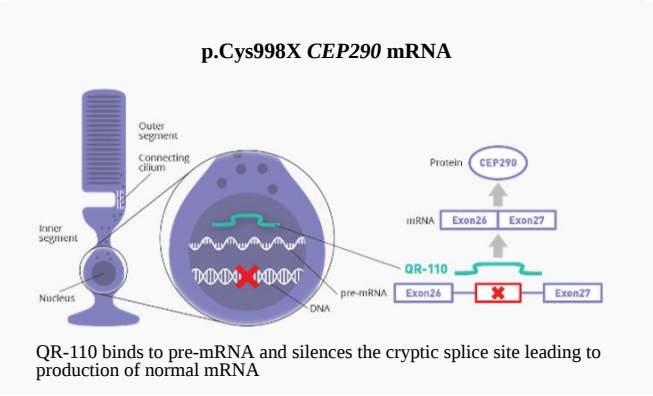
LCA Prevalence and Diagnosis

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. Vision impairment or blindness becomes obvious as age increases. After an 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 identified 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, 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 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 provided strong support for the clinical development and therapeutic potential of QR-110. We are currently conducting a Phase 1/2 study for QR-110 (PQ-110-001: NCT03140969) which commenced with the first patient dosed in November 2017.

PQ-110-001 is an open-label trial that will include approximately six children (age 6 - 17 years) and six adults (≥ 18 years) who have LCA 10 due to one or two copies of the p.Cys998X mutation in the *CEP290* gene. During the trial, subjects will receive four intravitreal injections of QR-110 into one eye; one every three months. The QR-110 trial is being conducted in three centers with significant expertise in genetic retinal disease in the U.S. and Europe. We expect to obtain six-month interim data from this study in 2018 and full twelve-month data in 2019.

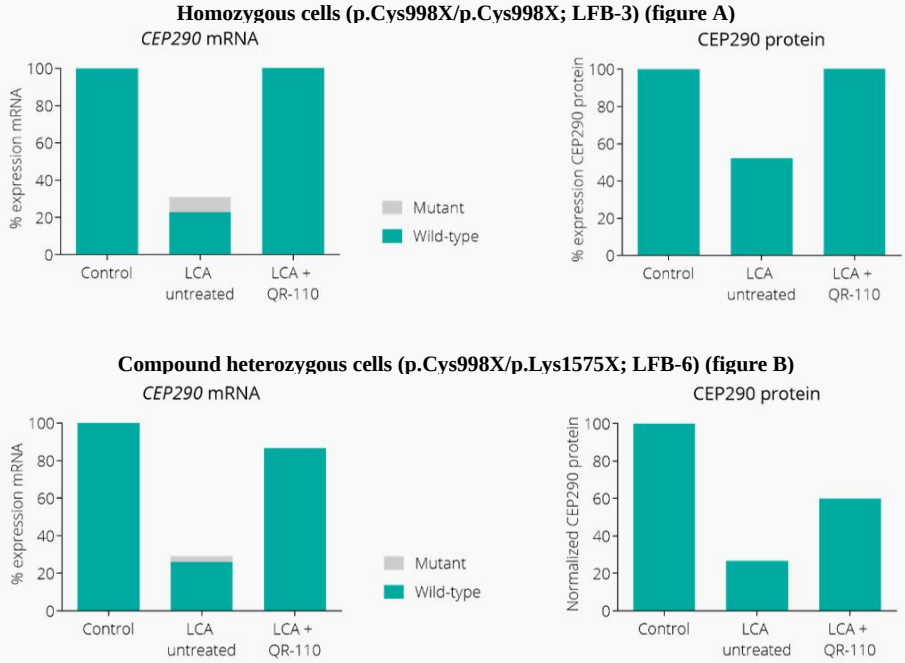
The primary objectives of the trial will be safety and tolerability. Secondary objectives will include the pharmacokinetics and restoration/improvement of visual function and retinal structure through ophthalmic endpoints such as visual acuity, full field stimulus testing (FST), optical coherence tomography (OCT), pupillary light reflex (PLR), mobility course and fixation stability.

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.



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 patients 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 fibroblasts 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. People 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.

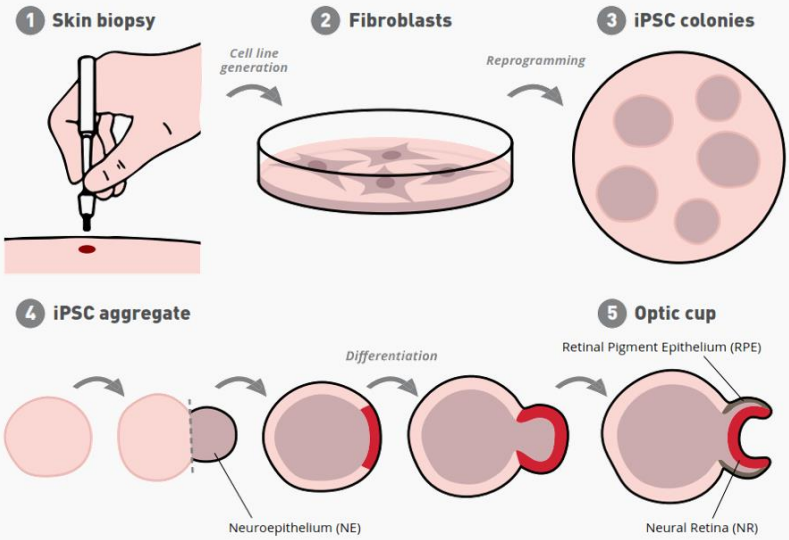
QR-110 activity in optic cup model

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.

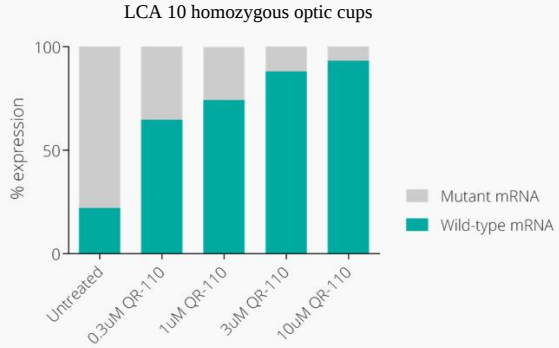
Optic cups constitute a convenient and clinically relevant model system to thoroughly study the mechanisms of inherited retinal degeneration since, unlike the classic cell models, these 3D organoids simulate the disease phenotype and provide an appropriate cellular model with the genetic mutations in 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 LCA 10 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.



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

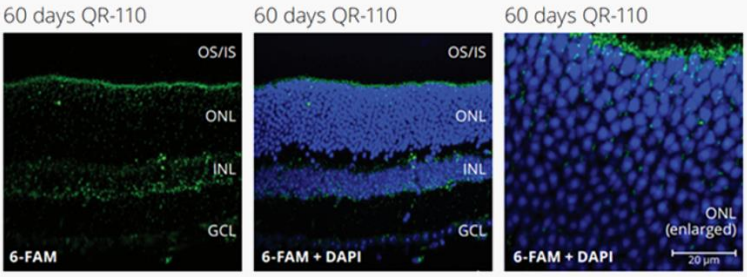


LCA 10 p.Cys998X homozygous patient fibroblasts were reprogrammed into iPSC which were differentiated into optic cups for 96 days and treated with different amounts of QR-110 for another 28 days (Parfitt et al. 2016) and analyzed using end-point PCR.

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.

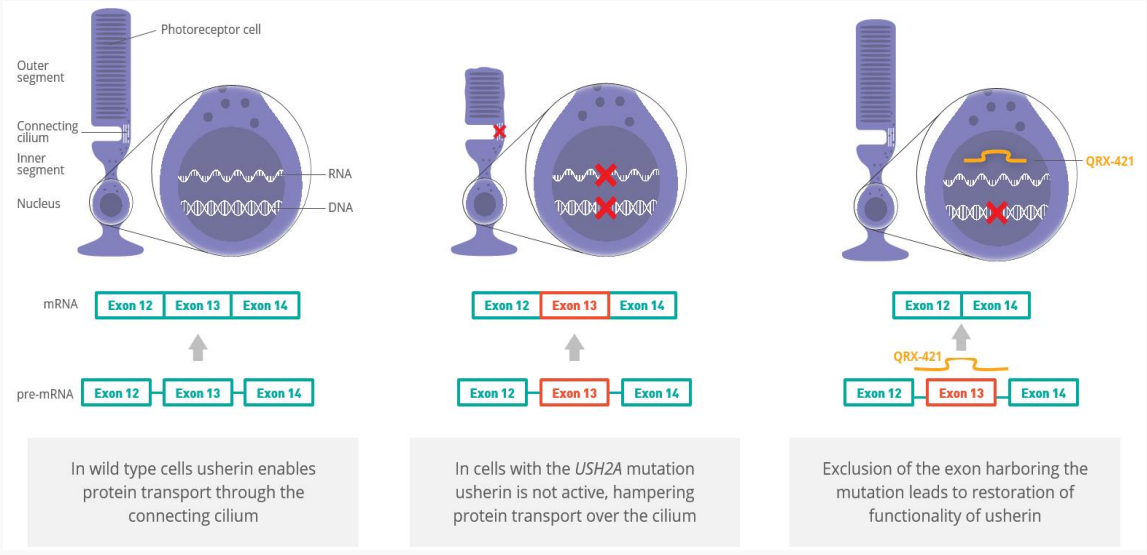
Usher Syndrome 2A

QR-421a and QR-411 for Usher Syndrome 2A

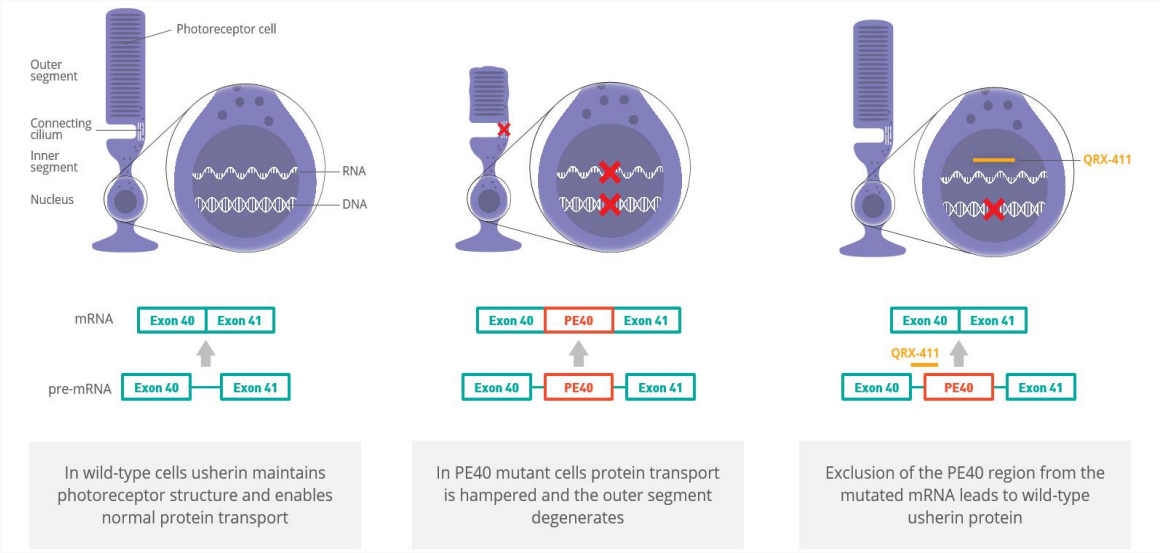
Usher syndrome is the leading cause of combined deafness and blindness. Patients with this syndrome generally progress to a stage in which they have very limited central and peripheral vision and moderate to severe deafness. The retinal phenotype, known as retinitis pigmentosa or RP, is characterized by photoreceptor degeneration that leads to progressive vision loss. Patients first experience defective dark adaption, loss of peripheral visual field when photoreceptor degeneration progresses, and eventually have only a residual central island of vision, which ultimately progresses to complete blindness. Like LCA, RP is a retinal ciliopathy.

Usher syndrome 2A is caused by mutations in the *USH2A* gene, encoding the protein usherin. Pathogenic mutations in the *USH2A* gene disrupt the production of usherin, a protein expressed in photoreceptors where it is required for their maintenance. Usherin is also expressed in the ear, where it is required for normal development of cochlear hair cells and hence, normal hearing. In the eye, defects in usherin cause RP. Our programs will target RP in patients with mutations in *USH2A* with Usher syndrome 2A as well as a subtype of non-syndromic retinitis pigmentosa, in which patients experience visual loss but do not suffer from hearing loss. Exon 13 mutations represent the most common mutations in the *USH2A* gene.

USH2A exon 13 splice correction



Splice correction for PE40 _USH2A_ mRNA



QR-421a is being developed as a treatment for RP caused by mutations in exon 13 of the *USH2A* gene. Pathogenic mutations in exon 13, including the prevalent c.2299delG, disrupt the production of usherin in retinal photoreceptors, where it is required for their maintenance. QR-421a aims to modify splicing of *USH2A* pre-mRNA such that the exon 13 is excised from the mature mRNA. The excision of exon 13 leads to an in-frame deletion in the *USH2A* mRNA. Since exon 13 encodes for a repetitive part of the usherin protein, excision of it leads to a fully functional usherin protein. Similar to approach of QR-110, QR-411 is targeted at correcting the splicing of a pseudoexon between exons 40 and 41.

In patients the specific c.7595-2144A>G (PE40) mutation leads to the aberrant inclusion of this pseudoexon in the mature mRNA and consequently a non-functional protein. Correction of the splicing pattern with QR-411 will lead to a fully functional usherin protein. It was observed that QR-421a and QR-411 reach the correct layer of the retina (the outer nuclear layer) after intravitreal administration to mice. Neither QR-421a nor QR-411 will be suitable for patients presenting with any other mutations involved in RP where they do not have at least one exon 13 mutated allele or a PE40 mutation targeted by QR-421a or QR-411 respectively.

Clinical Presentation of Usher Syndrome 2A

RP is characterized by limited visual field and the presence of visual defects such as reduced visual acuity, poor photo- and contrast sensitivity. The first visual symptoms often appear during the second decade of life and start with night blindness due to the start of degeneration of rod photoreceptors. When rod degeneration progresses, patients lose their peripheral visual field. Progression of rod degeneration continues with the degeneration of cones which eventually results in complete blindness. The rate and degree of vision loss vary within and among families. The diagnosis of the disease is based on clinical symptoms and ophthalmologic evaluations. Usher syndrome is both clinically and genetically a heterogeneous disease. Usher syndrome 2A is characterized by congenital moderate-to-severe bilateral hearing loss, the degree of hearing loss may become more severe over time. Individuals with Usher syndrome 2A present with progressive RP. In contrast with Usher syndrome types, Usher syndrome 2A patients do not suffer from vestibular dysfunction.

Disease Prevalence and Diagnosis

Although accurate prevalence figures do not exist, the number of patients with Usher syndrome 2A and non-syndromic retinitis pigmentosa due to *USH2A* exon 13 mutations is estimated to be around 16,000 in the Western World. In Europe, the PE40 mutation is present in approximately 3-7% of the total Usher syndrome 2A population providing us with an estimate of 1,000 patients. This number could be a considerable underestimate as many of these patients are unaware of the second disease causing allele following exome sequencing suggesting a causative mutation is intronic. While the hearing deficit in patients with Usher syndrome 2A can be at least partially restored using hearing aids or cochlear implants, there is no approved treatment for RP in Usher syndrome 2A and disease management is supportive.

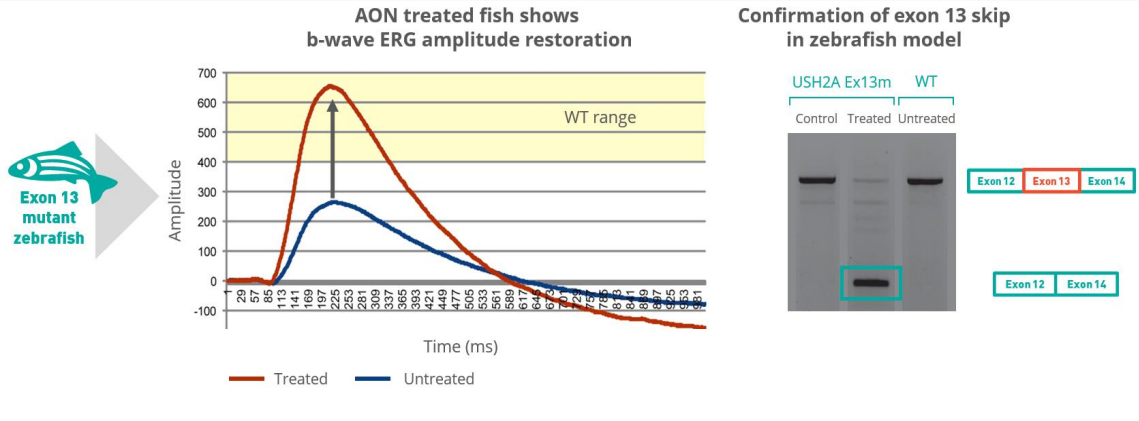
Approaches for the treatment of RP associated with Usher syndrome 2A

Vitamin A and docosahexaenoic acid (DHA) supplementations have been proposed as pharmacological treatment options. Both therapies have shown a good safety profile but limited clinical benefit. We believe QR-421a and QR-411 are the only product candidates in development for the treatment of patients with RP caused by mutations in exon 13 or PE40 mutations of the *USH2A* gene. Both QR-421a and QR-411 modulate splicing by enhancing exon-skipping which ultimately results in mature mRNA that can be translated into a shortened but functional usherin protein or a wild type *USH2A* mature mRNA and usherin protein. As RP is in most part a peripheral retinal disease, it is not particularly amenable to gene therapy approaches due to the need to administer viral vectors by sub-retinal injection and the due to the size of the *USH2A* gene, which is beyond the packaging limit of most viral vectors.

Pre-clinical evidence for QR-421a

- QR-421a-effected exon exclusion has been shown in a retinoblastoma cell line and two dimensional photoreceptor progenitor cells derived from primary fibroblasts of an *USH2A* c.2299delG homozygous patient.
- Uptake of QR-421a by human photoreceptor-like cells resulting in a biochemically demonstrable change in the *USH2A* pre-mRNA has been showed demonstrated with use of two dimensional photoreceptor progenitor cells.
- A zebrafish model carrying a mutation (premature stop codon) in exon 13 has been developed. The zebrafish model has been used to show that exon 13 skipping at the mRNA level results in restoration of usherin protein expression and restoration of electroretinogram (ERG) activity.

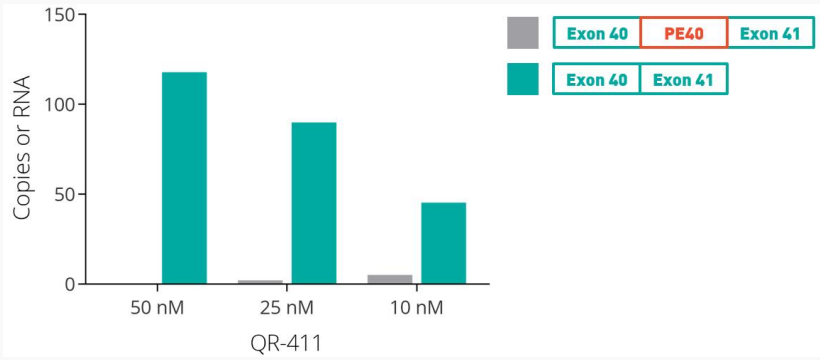
Exon-13 splicing oligos restore ERG in exon-13 mutant fish



Pre-clinical evidence for QR-411

- QR-411-effected exon exclusion has been shown in patient fibroblasts and two dimensional photoreceptor progenitor cells derived from primary fibroblasts of an *USH2A* c.7595-2144A>G (PE40) compound heterozygous patient.
- QR-411 demonstrates exon exclusion of human PE40 in a humanized *Ush2A* zebrafish mode.

QR-411 increases wild type *USH2A* mRNA



(1) Expression of wild type (blue bars) and PE40 (black bars) mRNA in a compound heterozygous patient fibroblast cell line carrying one allele containing the PE40 mutation and the other allele an exon 13 mutation (c.2391_2392del) after treatment with 10, 25, or 50 nM QR-411.

Clinical Development of QR-421a and QR-411

QR-421 and QR-411 are currently undergoing IND-enabling studies. We plan to advance the QR-421a program towards a Phase 1/2 clinical trial at the end of 2018. The clinical trial will consist of a single-dose arm and a six-month adaptive

multiple dose arm. We expect to receive top-line data from the single-dose arm in the first half of 2019 and from the adaptive multiple dose arm later in 2019.

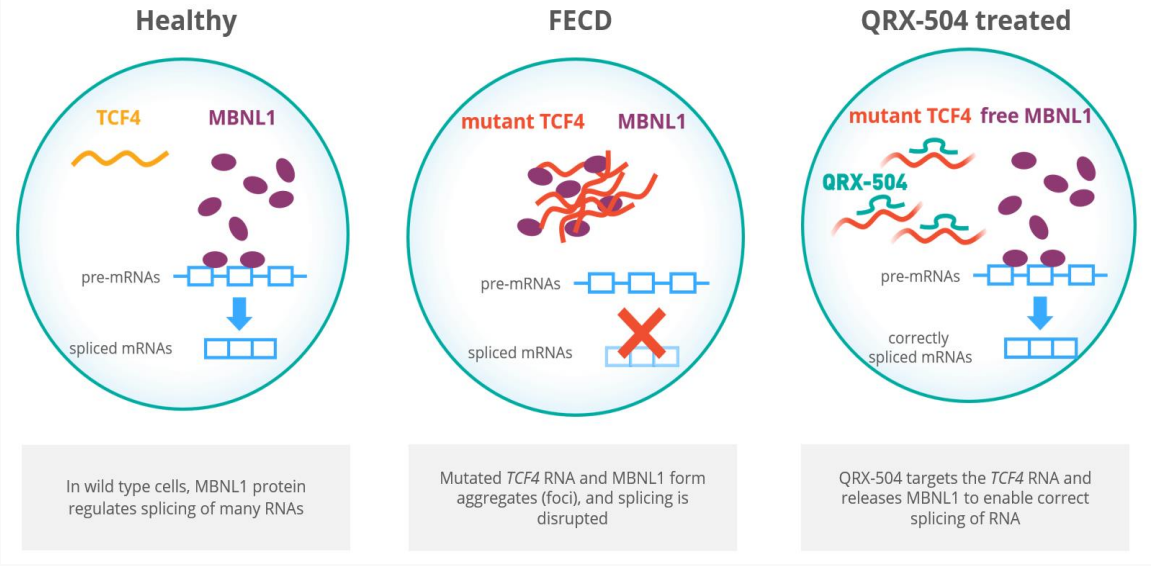
Research Grants

On February 9, 2018, we entered into an agreement with Foundation Fighting Blindness, or FFB, under which FFB will provide funding of $7.5 million to advance QR-421a into the clinic and will receive future milestone payments totaling $37.5 million, due in the three years after first sale of a commercial product.

Fuchs' Endothelial Corneal Dystrophy 3

Fuchs' endothelial corneal dystrophy 3 (FECD3) is a common, autosomal dominant, degenerative, age-related condition. The disease primarily affects the corneal endothelium, with characteristic focal outgrowths termed "guttae" and associated reduction in cell density. Progressive endothelial cell loss will ultimately lead to fluid accumulation, progressive corneal clouding, reduced visual acuity, and painful epithelial bullae. FECD3 is caused by a trinucleotide CTG repeat expansion situated within a non-coding, intronic region of the *TCF4* gene. Transcripts containing >50 copies of the repeat accumulate as nuclear RNA foci and are believed to sequester RNA-splicing factors, including the MBNL1 protein. This leads to a functional deficiency of these proteins and subsequent global disruption of mRNA splicing. QRX-504 is an antisense oligonucleotide which targets the trinucleotide repeat expansion leading to a reduction in splicing factor sequestration. It has been observed that following intraocular injection into mice, QRX-504 distributes within the corneal endothelium.

QRX-504 for FECD



Clinical Presentation of FECD3

Patients usually present with symptoms during their fifth to sixth decade. Early-stage disease is typically managed with topical hypertonic saline to reduce corneal swelling, but surgical intervention is currently the only treatment option available to patients with advanced disease.

Disease Prevalence and Diagnosis

It is estimated FECD affects more than 4% of individuals over the age 40 in the U.S, and similar prevalence is noted for other global regions. Patients usually present with guttae, a reduction in corneal endothelial cell density and corneal oedema. FECD3 is the major cause in patients in the Western world.

Approaches for the treatment FECD3

There are currently no treatment options for vision loss in patients with any form of FECD, other than corneal (endothelium) transplantation. This requires surgery where the damaged cornea is removed and replaced with a healthy donor cornea. 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.

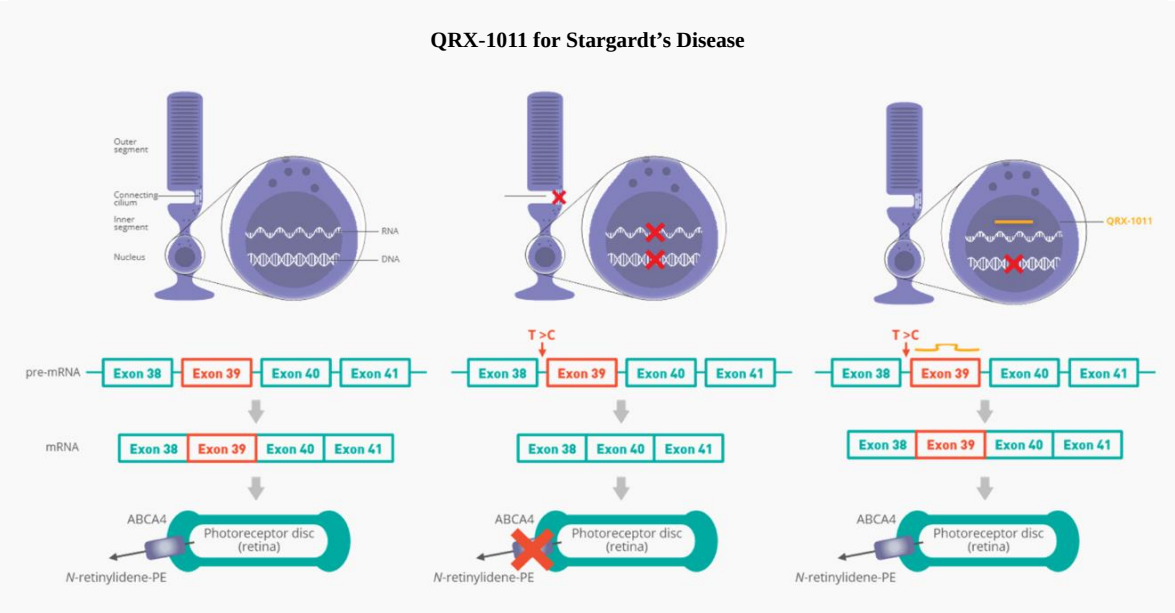
QRX-504 for the treatment of FECD3

QRX-504 aims to toxic gain of function *TCF4* mRNA releasing sequestered splicing factors and restoring endothelial cell homeostasis.

Stargardt's Disease

Stargardt's disease is the most common inherited macular dystrophy causing progressive impairment of central vision. It is associated with mutations in the *ABCA4* gene, encoding photoreceptor cell-specific ATP-binding cassette transporter 4 protein. The disease is inherited in an autosomal recessive fashion. The ABCA4 protein is predominantly expressed in the retina, where it is involved in transport of *N*-retinylidene-PE. Absence of ABCA4 results in the failure to clear these toxic substances, resulting in the loss in photoreceptor cells. A large number of disease-causing mutations have been found in *ABCA4*. c.5461-10T>C is the third most frequent *ABCA4* mutation, and causes a severe form of Stargardt's disease. This mutation is located in intron 38, and leads to skipping of exon 39, or of exon 39 and exon 40 in the mRNA. This aberrant splicing pattern results in reduced ABCA4 protein level. QRX-1011 targets the *ABCA4* pre-mRNA and results in the retention of exon 39 and exon 40, leading to the production of a mature wild type mRNA and protein.

QRX-1011 for Stargardt's Disease



Clinical Presentation of Stargardt's Disease

The most common symptom of Stargardt's disease is slow loss of central vision in both eyes. Onset of the disease is typically in childhood or young adulthood. Patients notice gray, black, or hazy spots in the center of their vision, have reduced light adaptation with increased light sensitivity, and some patients also experience color blindness as the disease progresses. Most patients with Stargardt's disease will progress to legal blindness or worse and may also suffer constriction of the visual field as they age.

Disease Prevalence

It is estimated there are 7,000 Stargardt's disease patients in the Western world with the c.5461-10T>C mutation in *ABCA4*.

Approaches for the treatment of Stargardt's disease

Currently, there is no treatment available for Stargardt's disease. Patients are often advised to wear eyeglasses or sunglasses that block UV light to reduce the possibility of additional eye damage caused by the sun and to avoid taking vitamin A supplements, but these measures do not prevent the progression of the disease. As Stargardt's disease due to the *ABCA4* c.5461-10T>C mutation is inherited in an autosomal recessive manner, the condition may be amenable to gene therapy approaches where the complete loss of ABCA4 function is complemented by simple gene replacement.

QRX-1011 for the treatment of Stargardt's disease

QRX-1011 is a first-in-class single-stranded oligonucleotide designed to treat vision loss caused by the specific c.5461-10T>C mutation in the *ABCA4* gene which leads to a splicing defect. Using an antisense oligonucleotide which modulates splicing of the mRNA, QRX-1011-mediated correction in the mRNA level leads to inclusion of the deleted exons and formation of functional, wild type ABCA4 protein which will potentially stop and perhaps reverse the progression of the disease.

Dystrophic Epidermolysis Bullosa (DEB)

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 has downstream effects such as wound infection, scarring, and SCC (squamous cell carcinoma). 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 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 a mutation in exon 73.

Diagnostic testing for DEB is based on 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.

Approaches for the Treatment of DEB

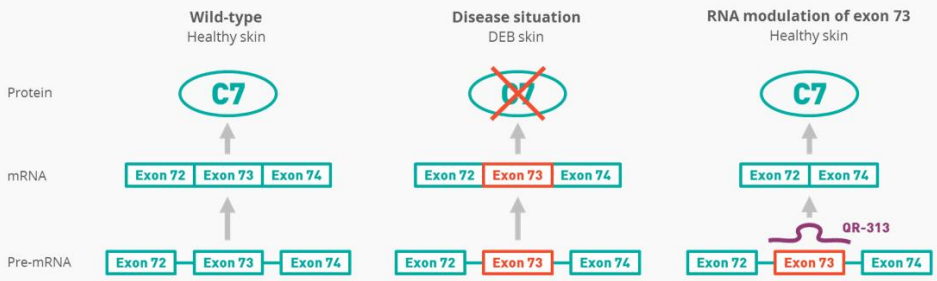
Currently, no disease modifying treatment is available for DEB. Palliative treatment is the only treatment available for DEB patients and constitutes a time-consuming daily activity. Palliative treatment primarily consists of care of (new) blisters by puncturing and draining to prevent further spread from fluid pressure, wound management to prevent infections, prevention of skin trauma to avoid new blister formation, and 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 focuses on topical delivery in the wounded skin of patients, with the aim to improve wound healing and reduce skin fragility. Therefore, we formulate QR-313 into a hydrogel for wound application that can be incorporated in the standard of care of patients.

Activity of QR-313 in cells and human skin equivalents

The activity of QR-313 was investigated in 3 different *in vitro* test systems; cell lines, primary cells, and human skin equivalents (HSEs). HSEs 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 blistering phenotype of DEB can be modeled.

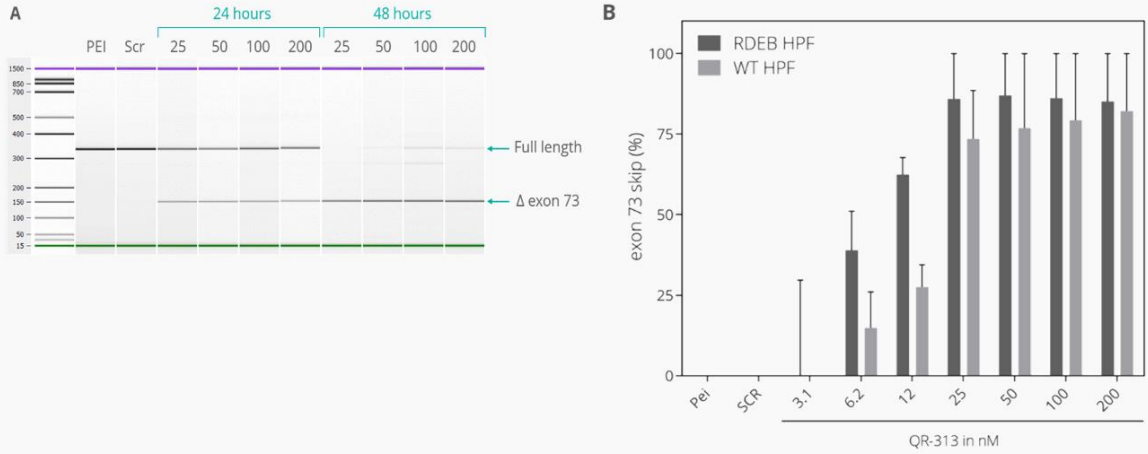
Experiments have shown

- Efficient exon 73 skip in the wild type (WT) fibroblast cell line (HeLa) as well as in in WT and mutant HaCaT keratinocytes in a dose-dependent manner
- Dose-dependent exon 73 skip in WT and RDEB patient Human Primary Fibroblasts (HPF) (Figure 1)
- Exon skip in HSEs after treatment with QR-313 using the same concentration, formulation and topical application as planned to use in patients (Figure 2)
- An increase in C7 expression in RDEB patient fibroblasts after treatment with QR-313 (Figure 3)
- Functionality of the shortened protein C7Δ73. It forms stable trimers, is present in anchoring fibrils at the dermal-epidermal junction, and binds its interacting partners collagen type IV and laminin-332.

The effect of QR-313 was assessed in HPFs from an RDEB patient, which contain one pathogenic mutation in exon 73 of *COL7A1* and another pathogenic mutation on the other allele. Results showed efficient skipping of exon 73 from *COL7A1* mRNA after 24 hours, and an increasing efficiency after 48 hours, with a near absence of the full length transcript that contains exon 73. In a subsequent set of experiments also lower concentrations were tested in RDEB HPFs as well as wild type HPFs. The results showed a clear dose response for QR-313 with increasing exon skip percentages in both RDEB and wild type HPFs. With the high doses of QR-313 a median skip of 77% for wild type and 87% for RDEB HPFs is reached.

Sequence analysis on the 150 bp product demonstrates removal of the complete exon 73 from the mRNA. This provides further evidence that QR-313 acts via its intended mode of action in human cells and efficiently skips exon 73 in the *COL7A1* mRNA.

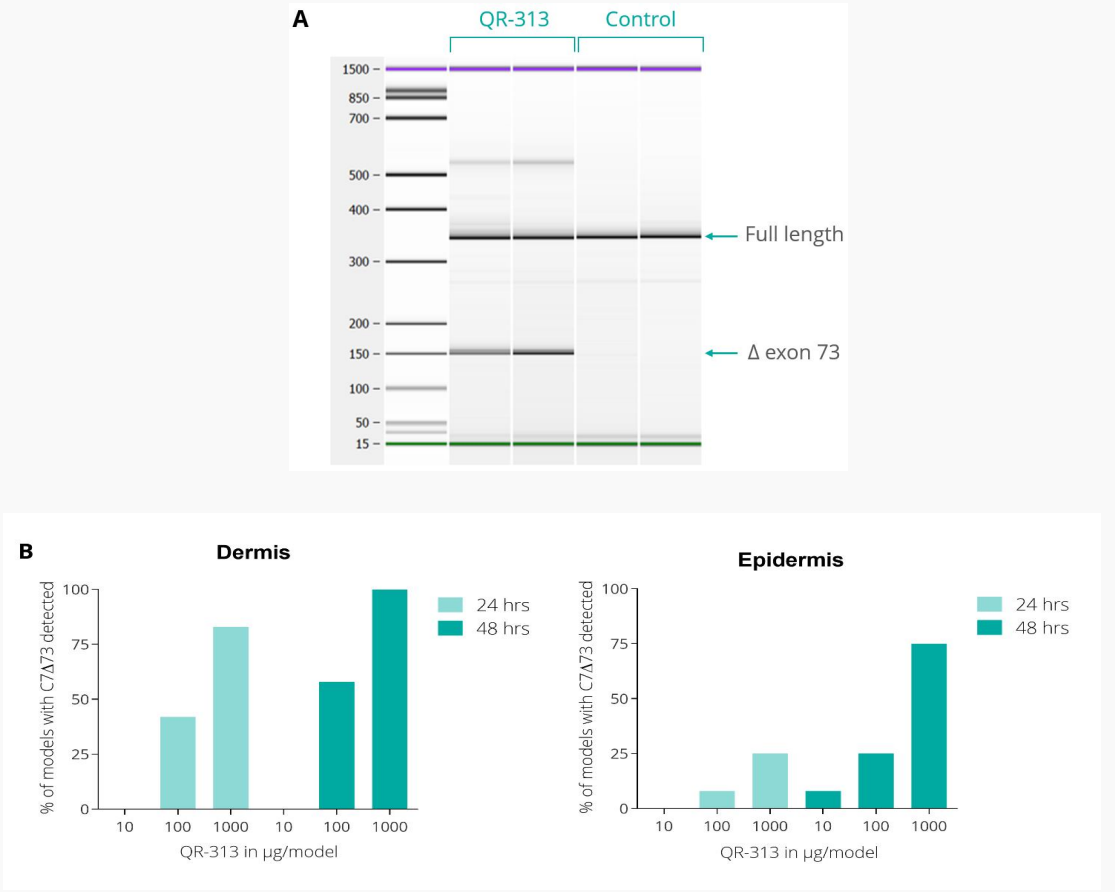
Exon 73 exclusion from *COL7A1* mRNA in RDEB and WT HPFs following treatment with QR-313



Splicing products of *COL7A1* mRNA following transfection with QR-313 or a scrambled version of QR-313 (SCR). Wild type HPFs and RDEB patient HPFs were transfected for 24 or 48 hours with 3.1 - 200 nM QR-313 or 100 nM scrambled. PEI transfection agent only was used as a negative control. Exon 73 skip in *COL7A1* mRNA was measured using RT-PCR. **A**. Representative Lab on a Chip result of exon 73 skip in RDEB HPFs. Treatment with SCR or PEI as negative control resulted in the production of a 350 bp fragment representing the wild type, full length amplicon (including exon 73) while treatment with QR-313 resulted in the production of a 150 bp fragment representing the modified mRNA product, which excludes exon 73 (Δ exon 73). The full length *COL7A1* band fades with increasing concentration or incubation time of QR-313, while the intensity of the Δ exon 73 band increases. **B**. Quantification of exon skip in wild type HPFs and RDEB HPFs after 24 hours of incubation. A dose-dependent increase in exon skip is observed from 3.1 to 50 nM. Higher concentrations do not further increase the exon skip percentage. Median and range of 3 independent experiments are shown.

In 3D models of the skin, so-called HSEs, the dose-response of Cy5-QR-313 was assessed in a range of 10-1000 µg by application in 200 mg carbomer hydrogel to HSEs wounds of approximately 2 cm2. The clinical situation was mimicked, so no transfection reagent was used. After 24 or 48 hours of incubation, RNA isolation was performed on both the dermal fibroblasts and the epidermal keratinocytes. The samples were analyzed for exclusion of exon 73 using RT-PCR. QR-313 activity was shown in RDEB-like wounded skin in both dermal fibroblasts and epidermal keratinocytes. In the dermal fibroblasts, exon 73 exclusion was shown in 40 and 80% of the models treated with 100 or 1,000 µg QR-313 for 24 hours, respectively. After 48 hours, exon exclusion was observed in 100% of the models in the dermal fibroblasts. In the epidermal keratinocytes, exon exclusion was shown in 10 and 30% of the models treated with 100 and 1,000 µg QR-313 for 24 hours, respectively. After 48 hours, models showing exon exclusion in keratinocytes increased to 30% and 80% for 100 µg and 1000 µg, respectively. After 24 hours exon skip was not detected in dermis or epidermis after treatment with 10 µg, while after 48 hours 8% of models showed exon skip in both dermis and epidermis.

Exon 73 skip in *COL7A1* mRNA in HSEs following treatment with Cy5-labelled QR-313



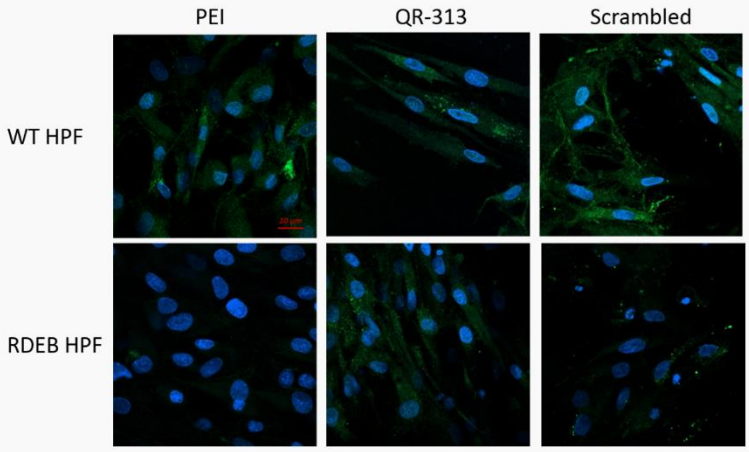
A. HSEs were treated for 24 hours with 50 µL of 0.5 mg/mL PBS formulation or 50 mg of the 0.5 mg/g carbomer gel formulation. RNA was then isolated from the dermal part of the model and RT-PCR analysis was performed. The different *COL7A1* mRNA products were analyzed for length. The 350 bp fragment represents the wild type, full length amplicon including exon 73 mRNA, while the 150 bp nucleotide fragment represents the exon skip *COL7A1* mRNA product Δ exon 73. **B**. HSEs were treated for 24 or 48 hours with carbomer gel formulated with a total dose of 10, 100 or 1000 µg Cy5-QR-313. After 24 or 48 hours incubation total RNA was isolated from both the dermal fibroblasts and epidermal keratinocytes separately. The graphs depict the percentage of models that demonstrate exon 73 exclusion for the dermal fibroblasts and epidermis. Data is representative of 2 different donors, 6 replicates per donor.

Following assessment of the *COL7A1* mRNA splice product, collage type VII (C7) protein production in compound heterozygous RDEB patient fibroblasts was assessed. Cells were seeded onto chamber slides and subsequently transfected with 100 nM QR-313 or scrambled QR-313 as a negative control using PEI as a transfection agent. The cells were fixed and stained for C7 protein 72 hours after transfection, and the nuclei were stained with DAPI before fluorescence imaging was performed.

After treatment with PEI alone, RDEB HPFs show minimal expression of C7 (the patient from which the cells were received has residual expression of the NC1 domain, against which the antibody is reactive), in contrast to WT HPFs, where C7 staining is clearly visible in the cytoplasm (pseudo-coloured in green). Seventy-two hours after transfection, C7 staining in the RDEB HPFs is observed in the cytoplasm similar to the staining in WT HPFs, confirming C7 protein

formation. In contrast, transfection with the scrambled did not result in an increase in C7 staining compared to PEI alone.

Immunofluorescent staining of C7 in WT HPFs and RDEB HPFs



WT HPFs or RDEB HPFs with a heterozygous mutation in exon 73 were transfected either only with PEI, with 100 nM QR-313 or with 100 nm scrambled QR-313. After 72 hours, cells were fixed and stained for C7 (green) using indirect immunofluorescence and with DAPI (blue) to visualize the nuclei. Scale bar indicates 20 µm.

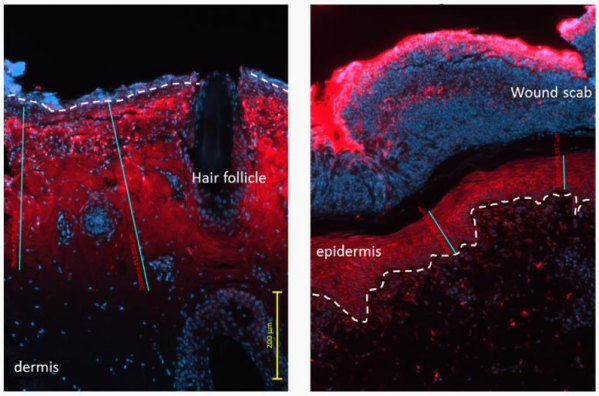
In vivo uptake

In vivo uptake of QR-313 in the skin was tested in Göttingen minipigs. The uptake and distribution of Cy5-labeled QR-313 formulated in a carbomer gel was tested after topical application on intact and wounded skin. Split-thickness wounds, which remove the epidermis and leave most of the dermis intact (2 cm by 3 cm and approximately 0.35 mm depth) were created on the backs of the animals using a dermatome. Cy5-labeled QR-313 DP (0.5 mg/g in 0.75% carbomer gel) was either applied as a single dose (SD) or multiple dose (MD) on days 1, 3 and 5. Skin biopsies were either taken 2 days after wounding (SD) or 7 days after wounding (MD) (this corresponds to 2 days after last dosing). Cy5-labeled QR-313 was not able to penetrate intact minipig skin.

Two days after the SD application on wounded skin, Cy5-labeled QR-313 had diffused into the dermis of the wound bed. For MD, Cy5-labeled QR-313 was still visualized in the wound bed after 7 days, however the depth of diffusion is reduced compared to the SD after 2 days. After 7 days, the epidermis had fully migrated over the wound bed (below the wound scab), and therefore the dermis was no longer exposed. The newly formed epidermis has taken up Cy5-labeled QR-313 and co-localization with the nucleus was observed using confocal microscopy imaging.

Delivery of Cy5-labeled QR-313 in wounded skin in Göttingen minipigs

Single dose | Multiple dose



Biopsy taken at day 2 | Biopsy taken at day 7

Histology sections of minipig skin 2 or 7 days after wounding. Left picture: skin exposed to Cy5-labelled QR-313 for 2 days after single dosing. Right picture: skin exposed to Cy5-labelled QR-313 after multiple dosing (3 administrations). Cy5-labelled QR-313 is depicted in red, nuclei are depicted in blue. White dotted line represents border between epidermis and dermis.

Planned Phase 1/2 Study for QR-313

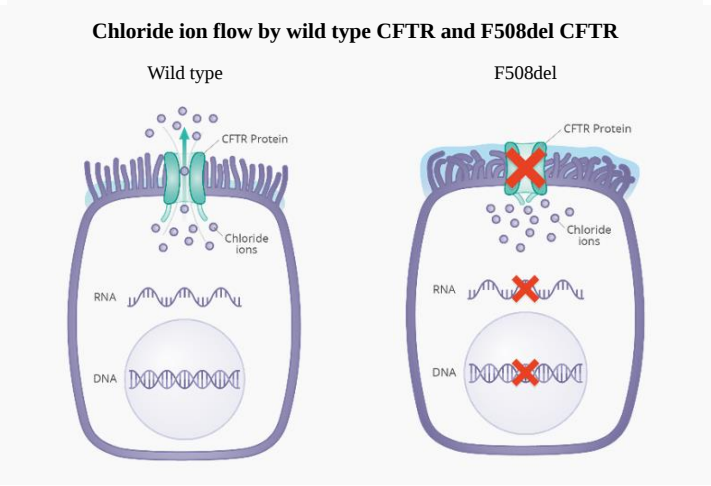
We are planning to commence our first in human study of QR-313 in DEB exon 73 patients in 2018, which we refer to as WINGS (A First in Human, Double-Blind, Randomized, Intra-Subject Placebo-Controlled, Multiple Dose Study of QR-313 Evaluating Safety, Proof of Mechanism, Preliminary Efficacy and Systemic Exposure in Subjects With Recessive Dystrophic Epidermolysis Bullosa (RDEB) due to Mutation(s) in Exon 73 of the *COL7A1* Gene). We plan to conduct the WINGS study as a Phase 1/2 safety and efficacy clinical trial in two parts, first enrolling eight RDEB patients with an exon 73 mutation, and after interim analyses expect to add another cohort of DEB patients. The study evaluates safety, tolerability and systemic passage of QR-313. The clinical trial is expected to be double blinded intra-patient controlled, single or dual-wound treatment for 4 weeks, with a follow-up period of 8 weeks. We expect to receive interim data from the first part of the trial in 2018 and full results in 2019. Beyond QR-313, we have a pipeline of discovery-stage programs for other mutations that cause DEB, including QRX-323 and QRX-333.

Cystic Fibrosis

Cystic Fibrosis Background

CF is the most common fatal inherited disease in the Western world and affects 77,000 patients. 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.

Chloride ion flow by wild type CFTR and F508del CFTR



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.

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 affect approximately 77,000 patients in the Western world. 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 "potentiator" molecule marketed under the trade name Kalydeco (ivacaftor). This product was approved by the FDA in 2012 to treat patients with the G551D 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. In March 2017, Vertex reported Phase 3 results of a new fixed-dose combination of tezacaftor and ivacaftor. This combination demonstrated clinical benefits of the same magnitude than Orkambi, but was better tolerated. A marketing application has been submitted in the United States and European Union. Commercialization is anticipated to begin in 2018. Approximately 12,000 US patients could be treated with Orkambi or with the tezacaftor-ivacaftor at an estimated annual cost of approximately $260,000 or more in addition to the cost of standard of care. In July 2017, Vertex reported preliminary results of next-generation correctors (VX-440, VX-152 and VX-659) being used in combination with tezacaftor and ivacaftor, to be developed as triple combination regimens. Data showed that such triple combinations improved lung function, sweat chloride and respiratory symptoms in CF patients with one or two copies of the F508del mutation. Data from ongoing Phase 2 trials are expected in the beginning of 2018. We believe these studies validate that F508del *CFTR* is a treatable target and indicate there is still a 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.

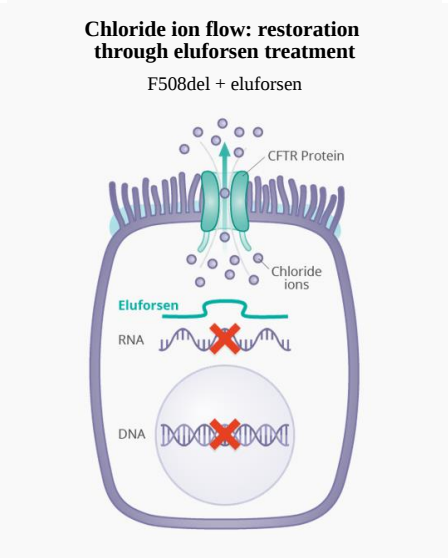
Our RNA Approach

Eluforsen 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. Eluforsen 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.

Eluforsen for Treatment of CF

We are developing eluforsen as an inhaled treatment for CF patients. Eluforsen is a single-stranded RNA oligonucleotide designed to restore CFTR function in CF patients with the F508del gene mutation. Eluforsen 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 eluforsen, which would be expected to result in restoration of chloride efflux.



Clinical Development for eluforsen

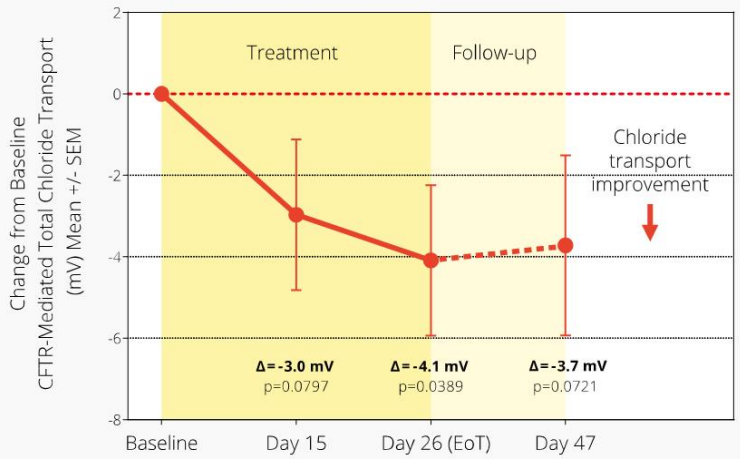
We conducted two clinical trials of eluforsen in parallel. Study PQ-010-002 is a proof-of-concept trial evaluating topical administration of eluforsen and its effect on the nasal potential difference (NPD), a biomarker of CFTR function. This trial opened for enrollment in September 2015 and was completed in September 2016. Study PQ-010-001 is a Phase 1b safety and tolerability trial. This trial opened for enrollment in June 2015 and was completed in September 2017.

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 eluforsen 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 eluforsen 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 eluforsen. 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. Eluforsen 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).

Final results were reported at the European Society of Cystic Fibrosis (ECFS) conference in June 2017. 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 that are 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. Eluforsen administered via the intranasal route was observed to be well tolerated.

Eluforsen 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 eluforsen 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 eluforsen clinical NPD results in perspective

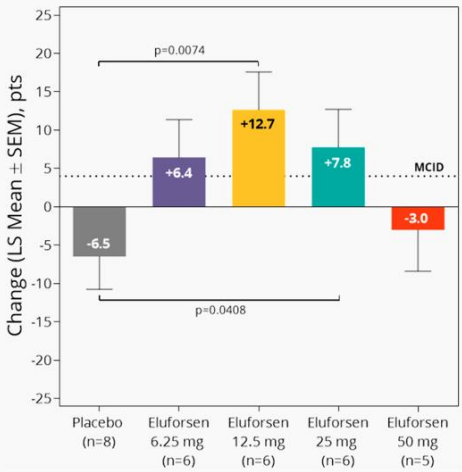
PQ-010-001 Phase 1b Safety and Tolerability Trial

This clinical trial was a Phase 1b, randomized, double-blind, placebo-controlled, 28-day dose-escalation trial to evaluate the safety, tolerability and pharmacokinetics of eluforsen. The trial enrolled CF patients that are homozygous for F508del and age 18 years and above. The trial was conducted at 26 sites located in 10 countries in North America and EU and enrolled 70 patients. The trial consisted of 4 single ascending dose cohorts and 4 multiple ascending dose cohorts (12 doses over 4 weeks). In each cohort of 8 patients, the randomization was 3:1, meaning that 6 patients received eluforsen and 2 patients received placebo.

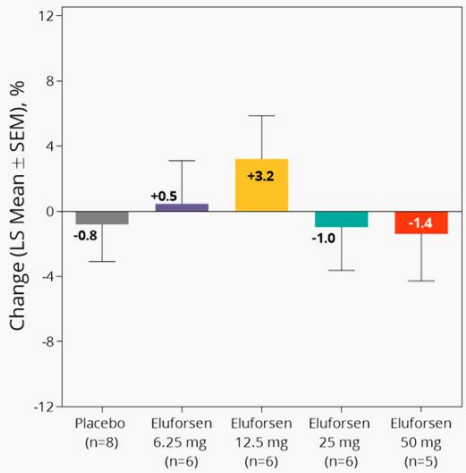
Eluforsen was given as a nebulized solution to the lower airways after chest physiotherapy, which is a standard procedure used with other currently administered inhaled medications. This method of drug administration is common in CF patients. The primary outcome measures were to characterize safety, tolerability and pharmacokinetics of eluforsen in CF patients. Pharmacokinetics was assessed in serum, urine and sputum to establish the safety and to give indications of uptake into the lung and systemic circulation in order to provide PK/PD information to design our future trials. We also assessed exploratory efficacy outcome measures, including lung function, sweat chloride levels, weight gain, as well as respiratory symptoms and quality-of-life measures specific to CF.

The results of the single-dose cohorts were reported in 2016 and all doses were safe and well-tolerated. In September 2017, we reported the preliminary results of the multiple-dose cohorts in which 36 subjects were enrolled. Eluforsen was observed to be safe and well-tolerated across all doses with no serious adverse events related to treatment. A clinically meaningful improvement of CF respiratory symptoms, as measured by CFQ-R RSS, was observed in 3 out of 4 multiple dose groups with a mean improvement of 13.0 to 19.2 points compared to placebo. The magnitude of the benefit observed in CFQ-R RSS for these dose groups exceeded the established minimal clinically important difference (MCID) of 4.0 points. In addition, a supportive trend of improved lung function was observed up to 4.0% mean absolute change in ppFEV1 compared to placebo. There were no changes in weight gain and sweat chloride.

Improvement in respiratory symptoms as measured by CFQ-R RSS at end of treatment



Change in lung function ($ppFEV_1$) at end of treatment



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 eluforsen 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 plan to commence this trial in 2018 subject to a potential partnership.

Besides our program for eluforsen 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 estimated 15% of the CF population, up to 12,000 patients in the Western world, with these programs.

Inhaled administration of eluforsen

To achieve broad distribution to CF-affected organs, we deliver eluforsen 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.

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 eluforsen. 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 eluforsen. In 2017, ProQR also received additional tranches totaling €0.3 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.

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 (tolerability) 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, eluforsen, 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 eluforsen product candidate. The granted European filing (EP 2852668 B1) was validated in all European Patent Convention contracting states. No opposition was filed after the nine-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 three 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 third U.S. patent covers the eluforsen product. The term of the first issued U.S. patent is expected to extend to October 2027, the term of the second issued U.S. patent is expected to extend to May 2025, and the term of the third U.S. patent is expected to extend to 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. Patents were granted in Europe (EP 2753694 B1) and in the U.S. (US 9,771,580) and applications are currently pending in the U.S. (continuation application) as well as Brazil, Canada, Australia, and Eurasia. The term of any patents resulting from these applications would be expected to extend to at least 2032. Furthermore, we entered into an exclusive license agreement with Inserm Transfert SA and Assistance-Publique-Hôpiteaux de Paris (AP-HP), Paris, France in January 2018 to obtain rights in a patent family with composition of matters claims directed to antisense oligonucleotides for treating LCA and method of treatment claims relating to modulation of the splicing of the *CEP290* gene product. Patents were granted in the U.S. (US 9,012,425; US 9,487,782; US 9,777,272) and applications are currently pending in the U.S. and Europe. The term of any patents resulting from these applications would be expected to extend to at least 2032.

To further strengthen our position on QR-110, we filed our own international patent application in February 2016 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 was continued in the U.S., Europe, China, and several other countries. 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 that were continued in the U.S., Europe, China, and several other countries. 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 Usher Program

With regard to our Usher program and our lead candidates in the Usher space, QR-411 and QR-421a, we filed two international patent applications in April and September 2017, and that are expected to be continued in national and regional patent applications in October 2018 and March 2019 respectively. The term of any patents resulting from these applications, if issued, would be expected to extend to at least 2037.

Patent Rights Relating to Our Axiomer Program

With regard to our Axiomer program, we filed several national and international patent applications from 2014 to 2017, and that are expected to be continued in national and regional patent applications after the respective international phases. The term of any patents resulting from these applications, if issued, would be expected to extend to at least 2038.

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 potentially up to $ 1,700,000 in additional payments upon the achievement of certain development and regulatory milestones, depending on the moment of achievement of such 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% or 5%, depending on the moment of NDA filing, 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.

License Agreements with Radboud University Medical Center

On April 17, 2014 ProQR Therapeutics and Radboud University Medical Center have entered into a Patent License Agreement in the field of antisense oligonucleotide-based therapy for Leber's Congenital Amaurosis, or LCA. Under the terms of this license agreement, we have an exclusive, world-wide royalty-bearing license under certain Radboud patent rights to develop, make, have made, use, sell offer for sale and import of certain licensed products of Radboud for use in all prophylactic and therapeutic uses in the field of LCA. Pursuant to the terms of the license agreement, we are obligated to pay Radboud net-sales-related royalties which shall be determined on a product-by-product and country-by-country basis. If we are required to pay any third party royalties, we may deduct that amount from that which is owed to Radboud. Radboud shall provide human resources, materials, facilities and equipment that are necessary for pre-clinical and clinical trials and if we do not purchase such trial facilities from Radboud, we are required to pay an increased net-sales-related royalty. In our sole discretion, we may elect to convert our obligation to pay net-sales-related royalties into one of the two lump-sum royalty options depending on whether we elect to convert prior to or after regulatory approval has been filed.

ProQR may sublicense our rights to any third-party provided such sub-license includes the same obligations on the sub-licensee as are on us and we promptly furnish Radboud with a copy of the executed sublicensing agreements.

The license agreement will remain in effect until the date on which all patent applications and all granted patents ensuing from such applications have expired or is terminated earlier in accordance with the agreement. Either party may terminate the agreement if the other party is in default of a material obligation under the agreement which has not been cured within 30 days of notice of such default. Either party may also terminate the agreement if the other party declares bankruptcy, dissolves, liquidates or the like. Radboud may also terminate the agreement if we do not pay any amount owed under the agreement and such payment remains overdue for at least 30 days after receiving notice from Radboud of the amount due.

In June 2015, we entered into another license agreement with Radboud University Medical Center, or Radboud. Under the terms of this license agreement, we have an exclusive, world-wide royalty-bearing license under certain Radboud patent rights to develop, make, have made, use, sell offer for sale and import of certain licensed products of Radboud for use in all prophylactic and therapeutic uses in the field of Usher syndrome. Pursuant to the terms of the license agreement, we are obligated to pay Radboud net-sales-related royalties which shall be determined on a product-by-product and country-by-country basis. If we are required to pay any third party royalties, we may deduct that amount from that which is owed to Radboud. Radboud shall provide human resources, materials, facilities and equipment that are necessary for pre-clinical and clinical trials and if we do not purchase such trial facilities from Radboud, we are required to pay an increased net-sales-related royalty. In our sole discretion, we may elect to convert our obligation to pay net-sales-related royalties into one of the two lump-sum royalty options depending on whether we elect to convert prior to or after regulatory approval has been filed.

ProQR may sublicense our rights to any third-party provided such sub-license includes the same obligations on the sub-licensee as are on us and we promptly furnish Radboud with a copy of the executed sublicensing agreements.

The license agreement will remain in effect until the date on which all patent applications and all granted patents ensuing from such applications have expired or is terminated earlier in accordance with the agreement. Either party may terminate the agreement if the other party is in default of a material obligation under the agreement which has not been cured within 30 days of notice of such default. Either party may also terminate the agreement if the other party declares bankruptcy, dissolves, liquidates or the like. Radboud may also terminate the agreement if we do not pay any amount owed under the agreement and such payment remains overdue for at least 30 days after receiving notice from Radboud of the amount due.

License Agreement with Inserm Transfert SA

In January 2017, we entered into a license agreement with Inserm Transfert SA and Assistance-Publique-Hôpiteaux de Paris. Under the terms of the agreement, we have world-wide, exclusive, royalty-bearing license under patent rights belonging to Inserm Transfert SA and other co-owners to develop, have developed, make, have made, use, have used and sell, have sold or otherwise distribute certain licensed products related to antisense oligonucleotides for treating LCA and method of treatment claims relating to modulation of the splicing of the CEP290 gene product.

We have the right to grant sublicenses to third parties subject to certain limitations such as the sublicensee's activities do not conflict with the public order or ethical obligations of Inserm Transfert SA or any co-owner and do not tarnish the image of Inserm Transfert SA or any co-owner.

In partial consideration of the rights and licenses granted by the license agreement, we are required to make payments upon the completion of certain milestones: completion of a clinical trial more advanced than First in Man, such as a phase IIb; and the first marketing authorization or any foreign equivalent for a first product. In further consideration of the rights and license granted under the agreement, we shall pay to Inserm Transfert SA a running royalty on net sales of products sold by us or our sublicensee.

Unless terminated earlier pursuant to termination provisions of Agreement, the license agreement will remain in effect on a country-by-country basis, until the later to occur of the following events (i) the invalidation or expiration of the last to expire or to be invalidated patent rights which covers the manufacture, use or sale of the product in said country or until the expiration of the exclusive commercialization right granted by a regulatory agency to a product as an orphan drug or (ii) five years after the first commercial sale of a product in the country in which the product is sold. The agreement may be terminated by either party in the event of an uncured breach by the non-breaching party. Inserm Transfert SA may terminate the agreement if we become the subject of voluntary or involuntary winding-up proceedings or judicial recovery, if we or our sublicensees interrupt development activities for at least one year, if we or our sublicensees interrupt commercialization for more than twelve months after the first commercialization in a country, if we do not commercialize a product within two years following our obtaining of marketing approval in a country, or if we or our sublicensees do not put a product into commercial use and do not keep products reasonably available to the public within twelve years of the effective date of the agreement.

Other License Agreements

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 September 12, 2017, we spun out this program into Amylon Therapeutics B.V., in which we maintain a majority ownership.

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 eluforsen solution for nebulization, QR-110 solution for intravitreal injection, QR-421a 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, biotechnology, 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, delivery, reliability, convenience of dosing, patient recruitment for clinical studies, 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.

Our competitors are working on similar technologies in the field of RNA modulation and RNA editing, but also in the field of gene editing and gene therapy as well as other types of therapies, such as small molecules, protein replacement or antibodies. The industry targeting hereditary ophthalmology indications is driven by gene therapy (Spark Therapeutics, AGTC, Sanofi, Oxford Biomedica), gene editing (Editas Medicine; ciberer), and other approaches, including retinal implants, cell therapies, optogenetics and prevention of photoreceptor degeneration.

In the field of DEB, a number of companies are seeking to identify and develop drugs. There are four general clusters of potential disease modifying treatments for RDEB: autologous gene therapies (Abeona, Fibrocell, King's College, Krystal Biotech and Holostem Terapie Avanzate), allogeneic cell therapies (Allogeneic Cell Therapies, University of Minnesota and King's College), RNA modulation therapies (University of Southern California) and protein replacement therapies (Phoenix Tissue Repair). In regards to palliative treatments, the therapies that are currently under development are symptomatic and focus on reducing a secondary EB manifestation (Amicus, Amryt, and Tarix Orphan).

In the field of cystic fibrosis, 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. 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. 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 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. 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, 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;
- manufacture of the medicinal product in accordance with Good Manufacturing Practice, or GMP, 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 reauthorize 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, the parameters to assess efficacy 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. 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 patients 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 i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, 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 an unmet medical need 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, guidance, 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 pharmaco-economic 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. In December 2017, President Trump signed into law the Tax Cuts and Jobs Act of 2017, which includes a repeal of the individual mandate under the Affordable Care Act. Additionally, in October 2017, President Trump signed an Executive Order directing federal agencies to review regulations applicable to association health plans and short-term health insurance, and announced that the administration would halt federal subsidies to insurance plans under the Affordable Care Act. It is possible that other repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage and/or in individuals having insurance coverage that provides less generous benefits. 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 2019 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 of the clinical trial application 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. 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 eluforsen 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. Orphan drug designations have been granted by the European Commission to eluforsen (EU/3/13/1195), QR-110 (EU/3/16/1641) and QR-313 (EU/3/17/1938).

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, 2017, 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%);
- Amylon Therapeutics B.V. (the Netherlands, 80%);
- ProQR Therapeutics I Inc. (United States, 100%).

ProQR Therapeutics N.V. is also statutory director of Stichting Bewaarneming Aandelen ProQR (“ESOP Foundation”) and has full control over this entity.

D. Property, plants and equipment

We lease facilities of approximately 3,950 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 was terminated on December 31, 2017. 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

To date, we have financed our operations primarily through our initial public and follow-on offerings, 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. In 2017, we raised gross proceeds of € 22.9 million from the issuance of 7,597,498 ordinary shares and € 4.3 million from the issue and sale of 976,477 ordinary shares through our ATM facility. At December 31, 2017, we had cash and cash equivalents of € 48,099,000. 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, 2017, 2016 and 2015, we incurred net losses of € 43,675,000, € 39,103,000 and € 20,832,000, respectively. At December 31, 2017, we had an accumulated deficit of € 119,370,000. 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 candidates eluforsen, QR-110 and QR-313, advance QR-421a 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, 2017 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).

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 $ 1.07 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 eluforsen.

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 eluforsen (ProQR: € 4.6 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. Both programs have ended at December 31, 2017. We expect to continue generating other income from grants in 2018.

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-110 for the treatment of LCA

  The research and development costs relating to our product candidate, QR-110, primarily consist of salaries 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-313 for the treatment of EB

  The research and development costs relating to our product candidate, QR-313, 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.

- Eluforsen for the treatment of CF

  The research and development costs relating to our product candidate, eluforsen, primarily consist of salaries 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.

- Other development programs

  Other research and development expenses mainly relate to QR-421a 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, 2017, 2016 and 2015, we incurred expenses of € 31,153,000, € 31,923,000 and € 23,401,000, respectively, on research and development.

Our research and development expense may vary substantially from period to period based on the timing of our research and development activities. Research and development expense is expected to moderately increase as we initiate and continue clinical trials for eluforsen, QR-110 and QR-313 and advance QR-421a and 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 eluforsen, QR-110, QR-313, QR-421a or any other product candidate that we may develop in the future.

Any of these variables with respect to the development of eluforsen, QR-110, QR-313, QR-421a 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 remain fairly stable in upcoming years.

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 2017, as we held deposits in US dollars, the depreciation of the U.S. dollar against our functional currency (Euro) had a negative impact on our result.

Income tax

Due to the operating losses incurred since inception the Company has no tax provisions as of December 31, 2017. 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. Also, no other transactions have occurred that would lead to a deferred tax position.

Results of Operations

Comparison of the periods ended December 31, 2017, 2016 and 2015

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

	Year ended December 31,		
	2017	2016	2015
	(€ in thousands)		
Other income	1,495	1,828	3,235
Research and development costs	(31,153)	(31,923)	(23,401)
General and administrative costs	(10,840)	(9,478)	(6,837)
Operating result	**(40,498)**	**(39,573)**	**(27,003)**
Finance income and expense	(3,175)	470	6,171
Corporate income taxes	(2)	—	—
Net loss (attributable to equity holders of the Company)	**(43,675)**	**(39,103)**	**(20,832)**
Other comprehensive income	151	(16)	1
Total comprehensive loss (attributable to equity holders of the Company)	**(43,524)**	**(39,119)**	**(20,831)**

Other income

For the periods ended December 31, 2017, 2016 and 2015, we had other income of € 1,495,000, € 1,828,000 and € 3,235,000, respectively. These amounts reflect the grant received in August 2014 from CFFT, the Horizon 2020 grant received from the European Commission in May 2015 and income generated by the sublease of our property.

Research and development costs

Research and development costs amounted to € 31,153,000 for the year ended December 31, 2017, in line with € 31,923,000 for the year ended December 31, 2016 and increased from € 23,401,000 for the year ended December 31, 2015. These costs were primarily related to our product candidates, eluforsen, QR-110, QR-313, QR-421a and our innovation unit. Our research and development expense is highly dependent on the development phases of our product candidates and is expected to stay at the same level, although it may fluctuate significantly from period to period.

The variances in research and development costs between the years ended December 31, 2017, 2016 and 2015 are mainly due to:

- costs we incurred on clinical trials for eluforsen, particularly in 2015 and 2016, decreasing in 2017 after completion of the clinical studies;
- costs we incurred on clinical trials for QR-110 and QR-313 in 2017;
- 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, particularly in 2016 compared to 2015. The number of full-time equivalent employees working on research and development increased from 72 at December 31, 2015 to 100 at December 31, 2016 and 96 at December 31, 2017;
- 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 eluforsen and QR-110 compounds in 2016 and QR-313 and QR-421a compounds in 2017, 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 € 10,840,000 for the year ended December 31, 2017 from € 9,478,000 for the year ended December 31, 2016 and € 6,837,000 for the year ended December 31, 2015. The increase was primarily related to:

- increased staff costs associated with the increase of our general and administrative staff from 27 full-time equivalent employees at December 31, 2015 to 33 full-time equivalent employees at December 31, 2016 and 34 full-time equivalent employees at December 31, 2017;
- 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, particularly in 2016, further increasing in 2017;
- increased costs for legal support, accounting and other consultancy costs, including costs incurred in preparation of offerings in 2017; 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 expenses of € 3,175,000 for the year ended December 31, 2017, as compared to a net finance income of € 470,000 for the year ended December 31, 2016 and € 6,171,000 for the year ended December 31, 2015. The financial income mainly reflects foreign exchange result 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, follow on offerings, ATM facility, private placements of equity securities, convertible loans 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, 2017, 2016 and 2015.

	Year ended December 31,		
	2017	2016	2015
	(€ in thousands)		
Net cash used in operating activities	(34,951)	(34,221)	(24,232)
Net cash used in investing activities	(121)	(2,539)	(1,324)
Net cash generated by financing activities	26,640	357	1,620
Net increase/(decrease) in cash and cash equivalents	**(8,432)**	**(36,403)**	**(23,936)**
Currency effect cash and cash equivalents	(2,669)	738	6,065
Cash and cash equivalents at the beginning of the period	59,200	94,865	112,736
Cash and cash equivalents at the end of the period	**48,099**	**59,200**	**94,865**

Net cash used in operating activities increased from € 24,232,000 in the year ended December 31, 2015 to € 34,221,000 in the year ended December 31, 2016 and € 34,951,000 in the year ended December 31, 2017. 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 € 1,324,000 in the year ended December 31, 2015 to € 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. Subsequently, limited investments were needed in 2017, resulting in net cash used in investing activities of € 121,000.

Net cash generated by financing activities decreased from € 1,620,000 in the year ended December 31, 2015 to € 357,000 in the year ended December 31, 2016, increasing to € 26,640,000 in the year ended December 31, 2017. In 2015 and 2016, cash generated by financing activities primarily included loans from a governmental body, totaling € 1,640,000 and € 370,000 respectively. In 2017, we raised gross proceeds of approximately € 22.9 million from the issuance of 7,597,498 ordinary shares and € 4.3 million from the issue and sale of 976,477 ordinary shares through our ATM facility.

Cash and Funding Sources

The table below summarizes our main sources of financing for the years ended December 31, 2017, 2016 and 2015.

	Equity Capital	Convertible Loans	Government Borrowing	Total
	(€ in thousands)			
Year ended December 31, 2015	—	—	1,640	1,640
Year ended December 31, 2016	—	—	370	370
Year ended December 31, 2017	25,685	650	301	26,636
Total	25,685	650	2,311	28,646

Our sources of financing in 2017 were our offering in July providing net proceeds of € 4,864,000, our offerings in November providing net proceeds of € 16,683,000 and the sale of shares through our ATM facility providing net proceeds of € 4,138,000. 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.

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 in one or more at-the-market offerings. At December 31, 2017, 976,477 shares had been sold pursuant to its current at-the-market offering program.

In March 2018, we entered into a convertible loan (the “Loan”), pursuant to which we borrowed an aggregate of €260,000 from the lender. The loan bears interest at a rate of 3% per annum. The outstanding principal and interest under the Loan is convertible into our ordinary shares upon the first to occur of the following events, at the election of the lender for (i) or (ii): (i) our public announcement of a strategic business partnership aimed at joint development of, or development by the partner of, our Huntington’s disease program, in which case the lender may convert the outstanding Loan amount into our ordinary shares at the then-prevailing trading price less a 25% discount; (ii) our public announcement of our decision to independently develop our Huntington’s disease program in the future, in which case the lender may convert the outstanding Loan amount into our ordinary shares at the then-prevailing trading price; or, (iii) on or around March 30, 2020 at the then-prevailing trading price plus a 25% premium. In no event are we required, nor are we permitted, to issue ordinary shares in an amount that exceeds 0.5% of the total number of ordinary shares outstanding immediately prior to the entry into the Loan. The Loan agreement restricts the lender’s ability to transfer the Loan, and prohibits the lender from entering into or engaging in any hedge, swap, short sale, derivative transaction or other agreement or arrangement that transfers any ownership of, or interests in, the Loan or our ordinary shares issued or issuable upon conversion of the Loan. The Loan and the ordinary shares issuable upon conversion of the Loan were issued in reliance on a private placement exemption from registration under the Securities Act of 1933, as amended.

At December 31, 2017, we had borrowings of € 7,244,000, which consisted of borrowings from a government body (€ 6,582,000) and convertible loans (€ 662,000). 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 into the second half of 2019. 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, 2017, 2016 and 2015:

	Year ended December 31,		
	2017	2016	2015
	(€ in thousands)		
Purchases of tangible fixed assets	82	2,433	1,441
Purchases of intangible assets	—	—	28
Total	**82**	**2,433**	**1,469**

To facilitate the growing needs of our company and accommodate the increased staff levels, we 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. Subsequently, investments in 2017 were limited.

Contractual Obligations and Commitments

The table below analyzes ProQR's undiscounted liabilities into relevant maturity groupings based on the remaining period at December 31, 2017 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, 2017				
Borrowings	1,960	980	5,981	—
Trade payables and other payables	6,534	—	—	—
Total	**8,494**	**980**	**5,981**	—

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.

The lease expenditure charged to the income statement for operating leases in 2017 amounts to € 2,103,000 (2016: € 1,849,000, 2015: € 703,000). The total commitment as at December 31, 2017 amount to € 4,919,000 (2016: € 7,283,000, 2015: € 9,150,000).

Patent license agreements

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 eluforsen, 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 which 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 Inserm Transfert SA and Assistance-Publique-Hôpiteaux de Paris 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 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.

Refer to Item 4.B: "Business Overview" for more details on patent license agreements.

Clinical support agreements

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 eluforsen.

Pursuant to the terms of the agreement, we are obligated to make a one-time milestone payment to CFFT of up to approximately $ 16 million, payable in three equal annual installments following the first commercial sale of eluforsen, 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 eluforsen exceed $ 500 million in a calendar year. Lastly, we are obligated to make a payment to CFFT of up to approximately $ 6 million if we transfer, sell or license eluforsen other than for certain clinical or development purposes, or if we enter into a change of control transaction prior to commercialization. However, the payment in the previous sentence may be set-off against the $ 16 million milestone payment. 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.

On February 9, 2018, we entered into an agreement with Foundation Fighting Blindness, or FFB, under which FFB will provide funding of $7.5 million to advance QR-421a into the clinic and will receive future milestones.

Pursuant to the terms of the agreement, we are obligated to make a one-time milestone payment to FFB of up to $ 37.5 million, payable in four equal annual installments following the first commercial sale of QR-421a, the first of which is due within 60 days following the first commercial sale. We are also obligated to make a payment to FFB of up to $ 15 million if it transfers, sells or licenses QR-421a other than for certain clinical or development purposes, or if we enter into a change of control transaction. However, the payment in the previous sentence may be set-off against the $ 37.5 million milestone payment. Either FFB 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 € 7,704,000 at December 31, 2017 (2016: € 8,856,000). Of these obligations an amount of € 6,094,000 is due in 2018, 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, 2017 to December 31, 2017 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. Dinko Valerio and 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	2021
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 and is also member of the Supervisory Board of Amylon Therapeutics B.V. 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 President and Chief Operating Officer of Kaleido Biosciences Inc. From January 2014 to December 2017, Ms Lawton served as the Chief

Operating officer of Aura Biosciences Inc. and 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 2017 she joined the board of directors of Magenta Therapeutics. She also served on the board of directors of Cubist Pharmaceuticals for three years until its acquisition by Merck &Co., Inc. in 2015 and on the board of directors of CoLucid Pharmaceuticals until its acquisition by Eli Lilly in 2017. 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, and was appointed chairman in 2017. 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.

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. In 2017 he joined the board of directors of Horizon Pharma. 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), myTomorrows (NL), Horizon Pharma (Ire) and lmmodulon (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 has been our founding Chief Executive Officer since our incorporation in 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 is our Chief Corporate Development Officer and General Counsel. 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 co-founder and advisor of Mytomorrows N.V., a Dutch life sciences company. 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
David Rodman	May 12, 1955	Executive Vice President of Research & Development
Gerard Platenburg	February 24, 1964	Chief Innovation Officer
Smital Shah	April 25, 1976	Chief Financial Officer
Robert Cornelisse	September 20, 1971	Chief People and Organization

David Rodman, M.D. is our Executive Vice President of Research & Development. Mr. Rodman joined ProQR in 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, Mr. Rodman 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, Mr. Rodman 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. Mr. Rodman 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.

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 a 12-year track record of management and leadership 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. Prior to Gilead, 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. During this time, Smital has helped raise over $1 billion in equity capital and over $7 billion in debt capital for emerging and established biotech companies as well advised on a variety of strategic transactions such as mergers, divestitures, asset sales, dividends, and royalty monetizations. Previously, Ms. Shah held various R&D focused roles at Johnson & Johnson. Ms. Shah has a bachelor's and master's degree in Chemical Engineering and an MBA degree from the University of California at Berkeley.

Robert Cornelisse has served as our Chief People and Organization since January 2017. Mr. Cornelise joined us in May 2014. He is an experienced and driven entrepreneur, a skilled people manager and used to develop and structure young organizations. Prior to joining us, Mr. Cornelisse founded Flinndal, a marketing and sales organization for health products in several European countries, where his role within the company was COO. Prior to Flinndal he invested in several other marketing and sales companies and always contributed to those companies in a role as COO. Mr. Cornelisse is responsible for our organizational structure and the well-being of our people.

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 2017 is set out in the table below:

	2017			
	Short term employee benefits	Post-employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. Dinko Valerio	36	—	87	123
Mr. Henri Termeer	28	—	160	188
Mr. Antoine Papiernik	76	—	—	76
Ms. Alison Lawton	31	—	99	130
Mr. Paul Baart	84	—	—	84
Mr. James Shannon	33	—	92	125
	288	—	**438**	**726**

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).

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 2017 of each current member of the management board:

	2017			
	Short term employee benefits	Post-employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. D.A. de Boer	570	8	622	1,200
Mr. R.K. Beukema	411	15	261	687
	981	**23**	**883**	**1,887**

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), Alison Lawton and James Shannon. 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 provision 2.1.8 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 provision 2.1.8 of the DCGC, with the exception of Mr. Dinko Valerio. 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) 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 provision 2.1.8 of the DCGC, with the exception of Mr. Dinko Valerio. 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, 2017, we had a total of 130.2 employees (converted to FTE). Of these employees, 96.2 were engaged in research and development and 34 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, 2017 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 31,921,865 ordinary shares outstanding as at December 31, 2017. 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, 2017, 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]	3,625,925	11.4 %
JDG B.V.[2]	2,786,550	8.7 %
Jennison Associates LLC[3]	2,653,552	8.3 %
Entities affiliated with Invus (Artal International S.C.A.)[4]	1,900,000	6.0 %
Belinda Termeer[5]	1,815,576	5.7 %
Supervisory Board Members and Management Board Members		
Dinko Valerio[6]	1,094,275	3.4 %
Antoine Papiernik[7]	3,625,925	11.4 %
James Shannon[8]	77,846	0.2 %
Alison Lawton[9]	28,197	0.1 %
Daniel de Boer[10]	1,337,006	4.2 %
René Beukema[11]	534,147	1.7 %
Paul Baart	—	— %
All supervisory board members and management board members as a group (7 persons) [12]	**6,697,396**	**21.0 %**

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. Based solely on the Schedule 13G/A filed by Sofinnova Capital VII FCPR on February 14, 2018.

2 JDG B.V. was created as a tax planning vehicle and is owned by three holders, Jeroen Voskamp, Daniel de Boer and Gerard Platenburg, in the following proportions, 26.5%, 38.2% and 35.3%, respectively. None of Messrs. Voskamp, de Boer or Platenburg controls the Reporting Person, and each of Messrs. Voskamp, de Boer or Platenburg have the right to direct voting and dispositive decisions solely with respect to their respective contributed shares. Mr. de Boer is a member of our management board. Mr. Platenburg is an executive officer of our company.

3 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 6, 2018.

4 The registered office of the entities affiliated with Invus (Artal International S.C.A.) is 750 Lexington Ave., 30th Floor, New York, NY 10022. Based solely on the Schedule 13G filed by Invus Public Equities, L.P. on February 9, 2018.

5 Consists of 1,730,714 ordinary shares and options to acquire 84,862 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017.

6 Consists of 588,457 ordinary shares and options to acquire 50,855 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017. Also includes 454,963 shares held by the Valerio family foundation, Stichting Administratiekantoor Endavit, for which Mr. Valerio is the managing director. The address of Stichting Administratiekantoor Endavit is Vlielandstraat 5, 1181 HZ, Amstelveen, the Netherlands.

7 Consists of 3,625,925 ordinary shares held by Sofinnova Capital VII FCPR. Antoine Papiernik may be deemed to have shared voting and investment power with respect to such shares as a managing partner of Sofinnova Partners SAS, the management company of Sofinnova Capital VII FCPR.

8 Consists of 61,538 ordinary shares and options to acquire 16,308 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017.

9 Consists of options to acquire 28,197 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017.

10 Consists of options to acquire 184,713 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017, and 1,152,293 ordinary shares held by JDG B.V., which share is owned and controlled by Daniel de Boer, our chief executive officer.

11 Consists of 346,239 ordinary shares and options to acquire 187,908 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017.

12 Consists of 5,376,376 ordinary shares and options to acquire 467,981 ordinary shares that are currently exercisable or will be exercisable within 60 days after December 31, 2017.

Holdings by U.S. Shareholders

As at December 31, 2017, approximately 92.9% of our ordinary 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, 2017, there have been no material transactions that are unusual in their nature or conditions with any of our related parties, except for transactions 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, 2017, 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
Year ended December 31, 2017	6.90	2.75
Quarterly highs and lows		
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
First quarter 2017	5.20	3.65
Second quarter 2017	5.45	4.60
Third quarter 2017	6.90	4.30
Fourth quarter 2017	4.97	2.75
Monthly highs and lows		
September 30, 2017	6.90	4.60
October 31, 2017	4.97	3.75
November 30, 2017	4.00	2.90
December 31, 2017	3.35	2.75
January 31, 2018	3.80	2.95
February 28, 2018	3.55	2.80

Since September 18, 2014, our ordinary shares have been listed on the NASDAQ Global Market under ticker symbol PRQR. On March 9, 2018, the closing price per share reported on the NASDAQ Global Market was $ 3.40.

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.

At December 31, 2017, 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. In February 2018, our shareholders approved an amendment of our articles of association to increase the authorized share capital to € 7,200,000, divided into 90,000,000 ordinary shares and 90,000,000 preferred shares. Aforesaid increase is effected on February 27, 2018. 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 May 10, 2017, 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 ordinary shares for general purposes and/or for mergers, demergers, acquisitions and other strategic transactions and alliances or a combination thereof of up to 30% of the Company's issued share capital plus for issuance under stock option plans of up to 15% of the Company's issued share capital minus any treasury shares for a period of five years from the date of the resolution.

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.

On May 10, 2017, our general meeting of shareholders adopted a resolution pursuant to which the aforesaid authorizations to issue shares and to limit and exclude preemptive rights was renewed. In this renewed authorization the Management Board was delegated the authority to resolve, subject to approval of the Supervisory Board, to, in accordance with applicable laws and NASDAQ listing rules: (a) issue of ordinary shares for general purposes and/or for mergers, demergers, acquisitions and other strategic transactions and alliances (or a combination thereof) up to 30% of the Company's issued share capital, plus for issuance under stock option plans up to 15% of the Company's issued share capital (minus any treasury shares), for a period of 5 years from the date of the resolution of the general meeting of shareholders; (b) grant rights to subscribe for ordinary shares as described under (a); and (c) limit or exclude the pre-emptive rights of holders of ordinary shares, for a period of 5 years from the date of the resolution of the general meeting of shareholders, which delegation shall include the authority to determine the price and further terms and conditions of any such share issuance or grant. The words “issued share capital” means the Company’s issued share capital from time to time. For the avoidance of doubt, in the context of the 30% authorization for general purposes and/or for mergers, demergers, acquisitions and other strategic transactions and alliances (or a combination thereof) the issued share capital includes treasury shares, if any.

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 May 10, 2017, our general meeting of shareholders adopted a resolution pursuant to which our management board will be authorized to acquire up to 10 % of our issued share capital plus, in case of a material reorganization of the capital structure of the Company an additional 10%,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).

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.

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.

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[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.

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*'). Irrespective of the actual income and capital gains realized, the annual taxable benefit of all the assets and allowable liabilities of a Dutch Resident Individual holder of ordinary shares who is taxed under this regime is set at a deemed return based on the fair market value of the assets reduced by the allowable liabilities on January 1 of each year. Depending on the aggregate amount of the fair market value of the assets reduced by the liabilities, the deemed return ranges from 2.87% up to 5.39% (2017). This deemed return is subject to income tax at a flat rate of 30%. Taxation only occurs if and to the extent the fair market value of the assets reduced by the liabilities exceeds a threshold (heffingvrij vermogen) of EUR 25,000 (or EUR 50,000 in case of a fiscal partnership). The deemed return will be adjusted annually.

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 does not qualify 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;
- S corporations;
- certain former citizens or long term residents of the United States;
- persons that received our shares as compensation for the performance of services;
- persons that acquire ordinary shares as a result of holding or owning our preferred shares;
- holders that own directly, indirectly, or through attribution 10% or more of the voting power or value our shares; and
- holders that have a "functional currency" other than the U.S. dollar.

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

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

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

- a citizen or resident of the United States;
- a corporation, or other entity that is treated as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States, any state thereof, or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income taxation regardless of its source; or

- a trust, if a court within the United States is able to exercise primary supervision over its administration and one or more U.S. persons have the authority to control all of the substantial decisions of such trust or has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a United States person.

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

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

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

Distributions

Subject to the discussion under "Passive Foreign Investment Company Considerations," below, the gross amount of any distribution (including any amounts withheld in respect of Dutch withholding tax) actually or constructively received by a U.S. holder with respect to ordinary shares will be taxable to the U.S. holder as a dividend to the extent of our current and accumulated earnings and profits as determined under U.S. federal income tax principles. Distributions in excess of earnings and profits will be non-taxable to the U.S. holder to the extent of, and will be applied against and reduce, the U.S. holder's adjusted tax basis in the ordinary shares. Distributions in excess of earnings and profits and such adjusted tax basis will generally be taxable to the U.S. holder as either long-term or short-term capital gain depending upon whether the U.S. holder has held our ordinary shares for more than one year as of the time such distribution is received. However, since we do not calculate our earnings and profits under U.S. federal income tax principles, it is expected that any distribution will be reported as a dividend, even if that distribution would otherwise be treated as a non-taxable return of capital or as capital gain under the rules described above. Non-corporate U.S. holders may qualify for the preferential rates of taxation with respect to dividends on ordinary shares applicable to long-term capital gains (i.e., gains from the sale of capital assets held for more than one year) applicable to qualified dividend income (as discussed below). The Company, which is incorporated under the laws of the Kingdom of the Netherlands, believes that it qualifies as a resident of the Netherlands for purposes of, and is eligible for the benefits of, the Convention between the United States of America and the Kingdom of the Netherlands for the Avoidance of Double Taxation and the Prevention of Fiscal Evasion with respect to Taxes on Income, signed on December 18, 1992, as amended and currently in force, or the U.S.-Netherlands Tax Treaty, although there can be no assurance in this regard. Further, the IRS has determined that the U.S.-Netherlands Tax Treaty is satisfactory for purposes of the qualified dividend rules and that it includes an exchange-of-information program. Therefore, subject to the discussion under "Passive Foreign Investment Company Considerations," below, if the U.S.-Netherlands Tax Treaty is applicable, such dividends will generally be "qualified dividend income" in the hands of individual U.S. holders, provided that certain conditions are met, including holding period and the absence of certain risk reduction transaction requirements are met. The dividends will not be eligible for the dividends-received deduction generally allowed to corporate U.S. holders.

A U.S. holder generally may claim the amount of Dutch income withholding tax withheld as either a deduction from gross income or a credit against U.S. federal income tax liability. However, the foreign tax credit is subject to numerous complex limitations that must be determined and applied on a case-by-case 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 from sources outside the United States 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 were not a PFIC during the 2017 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 a mark-to-market election (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. (In determining the average annual distribution, the portion of any excess distribution from a prior year that was allocated to the prior-year PFIC period is disregarded.) 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."

A U.S. holder may elect mark-to-market treatment, which may alleviate some of the adverse consequences of PFIC status. 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 on that market, the mark-to-market election will be available to a U.S. holder. U.S. Holders should consult their tax advisors to determine whether the mark-to-market election would be available and if so, what the consequences of making that election would be in their particular circumstances.

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.

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 P-1 or A2 for short-term and long-term, respectively by Moody's and A-1 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, 2017 there was a net liability in U.S. Dollars of € 2.4 million (2016: € 2.4 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, 2017, we had several loans with a fixed interest rate, totaling € 7,244,000 (2016: € 5,697,000).

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 into the second half of 2019. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Item 12: Description of Securities other that Equity Securities

A. Debt securities

Not applicable.

B. Warrants and rights

Not applicable.

C. Other securities

Not applicable.

D. American depositary shares

Not applicable.

Part II

Item 13: Defaults, Dividend Arrearages and Delinquencies

No matters to report.

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

No matters to report.

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, 2017). 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, 2017.

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, 2017. Based on this assessment, management concluded that the Company’s internal control over financial reporting was effective as at December 31, 2017.

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, 2017, 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 2.1.8 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. On September 25, 2017, we established a Dutch foundation named Stichting Bewaarneming Aandelen ProQR for holding shares in trust for employees, members of the Management Board and members of the Supervisory Board of the Company and its group companies who from time to time will exercise options under the Company's equity incentive plans. We have issued an aggregate of 3,330,225 ordinary shares to the foundation, with the nominal value of € 0.04 per share paid out of our reserves. Upon exercise of outstanding options, the foundation will transfer the appropriate number of ordinary shares underlying such exercise and the optionee will pay the appropriate exercise price to us as share premium. Our company is the sole director of the foundation, and the foundation is not permitted to receive dividends or to vote on the ordinary shares it will hold from time to time.

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 (incorporated by reference to Exhibit 1.1 to the Registrant's Annual Report on Form 20-F for the fiscal year ended December 31, 2016 (File No. 001-36622) filed on March 31, 2017)
1.2*	Amended Articles of Association of the Registrant effective as of February 19, 2018
2.1	Form of Registration Rights Agreement by and between the Registrant and the shareholders party thereto (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.1#	ProQR Therapeutics B.V. Stock Option Plan and forms of notice of grant thereunder (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.2#	ProQR Therapeutics N.V. Stock Option Plan and forms of notice of grant thereunder (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.3#	Form of Management Services Agreement by and between the Registrant and Daniel Anton de Boer (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.4#	Form of Management Services Agreement by and between the Registrant and René Beukema (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.5	Form of Call Option Agreement by and between the Registrant and Stichting Continuity ProQR Therapeutics (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 16, 2014)
4.6	Sublease of Office Accommodation dated as of September 5, 2013 by and between the Registrant and Pharming Technologies B.V. (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.7	Sublease Agreement dated as of April 1, 2013 by and between the Registrant and MicroSafe Laboratories (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)
4.8†	Exclusive Patent License Agreement dated as of May 29, 2012 by and between the Registrant and The General Hospital Corporation d/b/a Massachusetts General Hospital (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 16, 2014)
4.9†	Agreement dated as of August 1, 2014 by and between the Registrant and Cystic Fibrosis Foundation Therapeutics, Inc. (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on August 14, 2014)

Exhibit No.	Description
4.10#	Form of Indemnification Agreement for the Managing Directors, Supervisory Directors and officers of the Registrant (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form F-1 (File No. 333-198151) filed on September 8, 2014)
4.11†	License and Clinical Supply Agreement, dated as of October 8, 2014, between the Registrant and PARI Pharma GmbH (incorporated by reference to Exhibit 10.1 to the Registrant's Report of Foreign Private Issuer (File No. 001-36622) filed on October 9, 2014)
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 (incorporated by reference to Exhibit 4.12 to the Registrant's Annual Report on Form 20-F for the fiscal year ended December 31, 2016 (File No. 001-36622) filed on March 31, 2017)
4.13†††	Lease Agreement for the Registrant's facility in Zernikedreef in Leiden, the Netherlands (incorporated by reference to Exhibit 4.13 to the Registrant's Annual Report on Form 20-F for the fiscal year ended December 31, 2016 (File No. 001-36622) filed on March 31, 2017).
4.14††	License Agreement between Radboudumc as Licensor, and ProQR Therapeutics N.V. as Licensee dated as of April 17, 2014 (incorporated by reference to Exhibit 4.14 to the Registrant's Annual Report on Form 20-F for the fiscal year ended December 31, 2016 (File No. 001-36622) filed on March 31, 2017)
4.15*††	License Agreement between Inserm Transfert SA, Assistance-Publique- Hôpitaux de Paris, and ProQR Therapeutics N.V. as Licensee dated January 17, 2018
4.16*††	Letter Agreement between Foundation For Fighting Blindness Clinical Research Institute and ProQR Therapeutics IV B.V. dated as of February 9, 2018
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 30, 2018

PROQR THERAPEUTICS N.V.

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

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

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Report of the Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated statements of financial position of ProQR Therapeutics N.V. (“the Company”) as of December 31, 2017 and 2016, the related consolidated statements of profit or loss and comprehensive income, changes in equity, and cash flows for each of the three years in the period ended December 31, 2017, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with International Financial Reporting Standards as issued by the International Accounting Standards Board.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting 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.

Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ Deloitte Accountants B.V.

Amsterdam, the Netherlands

March 30, 2018

We have served as the Company's auditor since 2013.

PROQR THERAPEUTICS N.V.

Consolidated Statement of Financial Position

		December 31, 2017	December 31, 2016
		(€ in thousands)	
Assets			
Intangible assets	*7*	39	90
Property, plant and equipment	*8*	2,505	3,438
Non-current assets		**2,544**	**3,528**
Social security and other taxes	*9*	396	395
Prepayments and other receivables	*10*	2,064	2,420
Cash and cash equivalents	*11*	48,099	59,200
Current assets		**50,559**	**62,015**
Total assets		**53,103**	**65,543**
Shareholders' equity			
Share capital		1,457	934
Share premium		148,763	123,597
Reserves		8,513	4,338
Accumulated deficit		(119,370)	(75,733)
Equity attributable to owners of the Company	*12*	**39,363**	**53,136**
Non-controlling interests		(38)	—
Total equity		**39,325**	**53,136**
Liabilities			
Borrowings		5,284	5,697
Non-current liabilities	*13*	**5,284**	**5,697**
Borrowings		1,960	—
Trade payables		546	328
Social security and other taxes		1,019	312
Pension premiums		—	13
Deferred income		347	—
Other current liabilities		4,622	6,057
Current liabilities	*14*	**8,494**	**6,710**
Total liabilities		**13,778**	**12,407**
Total equity and liabilities		**53,103**	**65,543**

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,		
		2017	2016	2015
		(€ in thousands)		
Other income	*15*	1,495	1,828	3,235
Research and development costs	*16*	(31,153)	(31,923)	(23,401)
General and administrative costs		(10,840)	(9,478)	(6,837)
Total operating costs		(41,993)	(41,401)	(30,238)
Operating result		**(40,498)**	**(39,573)**	**(27,003)**
Financial income and expense	*18*	(3,175)	470	6,171
Result before corporate income taxes		**(43,673)**	**(39,103)**	**(20,832)**
Corporate income taxes	*19*	(2)	—	—
Result for the year		**(43,675)**	**(39,103)**	**(20,832)**
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		151	(16)	1
Total comprehensive loss (attributable to equity holders of the Company)		**(43,524)**	**(39,119)**	**(20,831)**
Result attributable to				
Owners of the Company		(43,637)	(39,103)	(20,832)
Non-controlling interests		(38)	—	—
		(43,675)	**(39,103)**	**(20,832)**
Share information	*20*			
Weighted average number of shares outstanding		25,374,807	23,346,507	23,343,262
Earnings per share for result attributable to the equity holders of the Company (expressed in Euro per share)				
Basic and diluted loss per share		€ (1.72)	€ (1.67)	€ (0.89)

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

PROQR THERAPEUTICS N.V.

Consolidated Statement of Changes in Equity

	Attributable to Equity Holders of the Company							
	Share Capital (€ in thousands)	Share Premium (€ in thousands)	Equity Settled Employee Benefit Reserve (€ in thousands)	Translation Reserve (€ in thousands)	Accumulated Deficit (€ in thousands)	Total (€ in thousands)	Non-controlling Interests (€ in thousands)	Total Equity (€ in thousands)
Balance at January 1, 2015	**934**	**123,581**	**687**	—	**(15,798)**	**109,404**	**—**	**109,404**
Result for the year	—	—	—	—	(20,832)	(20,832)	—	(20,832)
Other comprehensive income	—	—	—	1	—	1	—	1
Recognition of share-based payments	—	—	1,212	—	—	1,212	—	1,212
Shares options exercised	—	14	—	—	—	14	—	14
Balance at December 31, 2015	**934**	**123,595**	**1,899**	1	**(36,630)**	**89,799**	**—**	**89,799**
Result for the year	—	—	—	—	(39,103)	(39,103)	—	(39,103)
Other comprehensive income	—	—	—	(16)	—	(16)	—	(16)
Recognition of share-based payments	—	—	2,454	—	—	2,454	—	2,454
Shares options exercised	—	2	—	—	—	2	—	2
Balance at December 31, 2016	**934**	**123,597**	**4,353**	**(15)**	**(75,733)**	**53,136**	**—**	**53,136**
Result for the year	—	—	—	—	(43,637)	(43,637)	(38)	(43,675)
Other comprehensive income	—	—	—	151	—	151	—	151
Recognition of share-based payments	—	—	4,024	—	—	4,024	—	4,024
Issue of ordinary shares	343	25,342	—	—	—	25,685	—	25,685
Issue of treasury shares	180	(180)	—	—	—	—	—	—
Shares options exercised	—	4	—	—	—	4	—	4
Balance at December 31, 2017	**1,457**	**148,763**	**8,377**	**136**	**(119,370)**	**39,363**	**(38)**	**39,325**

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

PROQR THERAPEUTICS N.V.

Consolidated Statement of Cash Flows

	Year Ended December 31,		
	2017	2016	2015
	(€ in thousands)		
Cash flow from operating activities			
Net loss	(43,675)	(39,103)	(20,832)
Adjustments for:			
Amortization & depreciation	1,065	1,245	480
Share-based payment expenses	4,024	2,454	1,212
Financial income and expense	3,175	(470)	(6,171)
Net foreign exchange gain / (loss)	151	(16)	1
Changes in working capital	164	1,433	637
Corporate income tax paid	(2)	—	—
Interest received	147	236	441
Net cash used in operating activities	**(34,951)**	**(34,221)**	**(24,232)**
Cash flow from investing activities			
Purchases of intangible assets	—	—	(28)
Purchases of property, plant and equipment	(121)	(2,539)	(1,296)
Net cash used in investing activities	**(121)**	**(2,539)**	**(1,324)**
Cash flow from financing activities			
Proceeds from issuance of shares, net of transaction costs	25,685	—	—
Proceeds from exercise of share options	4	2	14
Proceeds from borrowings	301	370	1,640
Proceeds from convertible loans	650	—	—
Redemption of financial lease	—	(15)	(34)
Net cash generated by financing activities	**26,640**	**357**	**1,620**
Net increase/(decrease) in cash and cash equivalents	**(8,432)**	**(36,403)**	**(23,936)**
Currency effect cash and cash equivalents	(2,669)	738	6,065
Cash and cash equivalents at the beginning of the year	59,200	94,865	112,736
Cash and cash equivalents at the end of the year	**48,099**	**59,200**	**94,865**

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, 2017, 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%);
- Amylon Therapeutics B.V. (the Netherlands, 80%);
- ProQR Therapeutics I Inc. (United States, 100%).

ProQR Therapeutics N.V. is also statutory director of Stichting Bewaarneming Aandelen ProQR ("ESOP Foundation") and has full control over this entity.

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 and the ESOP Foundation.

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 2017 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 as stated above, 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

Grant income is not recognized until there is reasonable assurance that the Company will comply with the conditions attached to them. Grants are recognized in profit or loss on a systematic basis over the period the Company recognizes as expenses the related costs for which the grants are expected to compensate.

(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, 2017, 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 has power over the entity, 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 Group reassesses whether or not it controls an entity if facts and circumstances indicate that there are changes to one or more of these elements. 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) Non-controlling interests ("NCI")

NCI are measured at their proportionate share of the acquiree's identifiable net assets at the acquisition date. Changes in the Group's interest in a subsidiary that do not result in a loss of control are accounted for as equity transactions.

(iii) 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.

(iv) 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 on a systematic basis over the period the Company recognizes as expenses the related costs for which the grants are expected to compensate.

(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 recognized on a net basis within the labor costs. Subsidies relating to labor costs are deferred and recognized in the income statement in 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 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 employees have rendered the service entitling them to the contributions. 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.

Compound financial instruments

Compound financial instruments issued by the Group comprise convertible notes denominated in euro that can be converted to share capital at the option of the holder, when the number of shares to be issued is fixed and does not vary with changes in fair value.

The liability component of a compound financial instrument is recognised initially at the fair value of a similar liability that does not have an equity conversion option. The equity component is recognised initially at the difference between the fair value of the compound financial instrument as a whole and the fair value of the liability component. Any directly attributable transaction costs are allocated to the liability and equity components in proportion to their initial carrying amounts.

Subsequent to initial recognition, the liability component of a compound financial instrument is measured at amortised cost using the effective interest method. The equity component of a compound financial instrument is not remeasured.

Interest related to the financial liability is recognised in profit or loss. On conversion, the financial liability is reclassified to equity and no gain or loss is recognised.

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 January 1, 2018, 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 January 1, 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 January 1, 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 January 1, 2019, with early adoption permitted and is expected to have an effect on our balance sheet of approximately € 5 million.

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, 2017 there was a net liability in U.S. Dollars of € 0.7 million (2016: € 2.4 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 weakening of the U.S. Dollar by 10% against all other currencies at December 31, 2017 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 (2016: € 2.5 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 several loans with fixed interest rates, totaling €7,244,000 at December 31, 2017 (2016: € 5,697,000). 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 held 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 A2 or A at a minimum by at least one NRSRO).

At December 31, 2017 and December 31, 2016, substantially all of our cash and cash equivalents were held at three large institutions, Rabobank, ABN Amro and 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, 2017				
Borrowings	1,960	980	5,981	—
Trade payables and other payables	6,534	—	—	—
Total	**8,494**	**980**	**5,981**	—
At December 31, 2016				
Borrowings	—	1,839	4,860	—
Trade payables and other payables	6,710	—	—	—
Total	**6,710**	**1,839**	**4,860**	—

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 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, 2016			
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**
Additions	—	—	—
Amortization	—	(51)	(51)
Movement for the period	—	**(51)**	**(51)**
Balance at December 31, 2017			
Cost	39	152	191
Accumulated amortization	—	(152)	(152)
Carrying amount	**39**	**—**	**39**

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 2017 is included in the general and administrative costs for an amount of €51,000 (2016: € 51,000).

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, 2016				
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**
Additions	9	47	26	82
Depreciation	(294)	(409)	(312)	(1,015)
Disposals	—	—	—	—
Movement for the period	**(285)**	**(362)**	**(286)**	**(933)**
Balance at December 31, 2017				
Cost	1,856	2,004	1,309	5,169
Accumulated depreciation	(802)	(1,069)	(793)	(2,664)
Carrying amount	**1,054**	**935**	**516**	**2,505**

The depreciation charge for 2017 is included in the research and development costs for an amount of € 836,000 (2016: € 907,000) and in the general and administrative costs for an amount of € 179,000 (2016: € 264,000).

9. Social Security and Other Taxes

	December 31, 2017	December 31, 2016
	(€ in thousands)	
Value added tax	396	395
Wage tax	—	—
	396	395

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

10. Prepayments and Other Receivables

	December 31, 2017	December 31, 2016
	(€ in thousands)	
Prepayments	1,991	1,250
Other receivables	73	1,170
	2,064	2,420

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

11. Cash and Cash Equivalents

	December 31, 2017	December 31, 2016
	(€ in thousands)	
Cash at banks	48,099	56,354
Bank deposits	—	2,846
	48,099	59,200

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 2017 Ordinary	Number of shares 2016 Ordinary	Number of shares 2015 Ordinary
Balance at January 1	23,346,856	23,345,965	23,338,154
Issued for cash	8,573,975	—	—
Exercise of share options	1,034	891	7,811
Treasury shares issued	4,503,149	—	—
Balance at December 31	**36,425,014**	**23,346,856**	**23,345,965**

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, 2017, 36,425,014 ordinary shares were issued and fully paid in cash, of which 4,503,149 were held by the Company as treasury shares (2016: 1,173,958).

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 (€ 166,764,000) 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 (€ 50,029,000) of its ordinary shares that may be issued and sold under a sales agreement in one or more at-the-market offerings. In 2017, the Company has issued 976,477 shares pursuant to its current at-the-market offering program, resulting in proceeds of € 4,138,000, net of € 127,000 of offering expenses.

On June 28, 2017, the Company agreed to the issuance of 1,200,000 ordinary shares to institutional investors at an issue price of $ 5.00 (€ 4.40) per share in a registered direct offering with gross proceeds of € 5,278,000. The closing of the offering was effected on July 3, 2017. Transaction costs amounted to € 414,000, resulting in net proceeds of € 4,864,000.

In November 2017, the Company consummated an underwritten public offering and concurrent registered direct offering of 6,397,498 ordinary shares at an issue price of $ 3.25 (€ 2.76) per share. The gross proceeds from both offerings amounted to € 17,671,000 while the transaction costs amounted to € 988,000, resulting in net proceeds of € 16,683,000.

(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'. On September 25, 2017, we established a Dutch foundation named Stichting Bewaarneming Aandelen ProQR for holding shares in trust for employees, members of the Management Board and members of the Supervisory Board of the Company and its group companies who from time to time will exercise options under the Company's equity incentive plans.

(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 € 4,024,000 in 2017 (2016: € 2,454,000, 2015: € 1,212,000), of which € 2,059,000 (2016: € 1,480,000, 2015: € 801,000) was recorded in general and administrative costs and € 1,965,000 (2016: € 974,000, 2015: € 411,000) was recorded in research and development costs based on employee allocation.

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 2017	Options granted in 2016	Options granted in 2015
Risk-free interest rate	1.913 %	1.467 %	1.497 %
Expected dividend yield	— %	— %	— %
Expected volatility	88.7 %	86.3 %	86.8 %
Expected life in years	5 years	5 years	5 years

The resulting weighted average grant date fair value of the options amounted to € 3.21 in 2017 (2016: € 3.72, 2015: € 10.35). 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:

	2017		2016		2015	
	Number of options	Average exercise price	Number of options	Average exercise price	Number of options	Average exercise price
Balance at January 1	2,205,989	€ 4.88	1,108,935	€ 4.19	998,765	€ 2.78
Granted	1,199,447	€ 4.63	1,214,126	€ 5.49	125,798	€ 15.27
Forfeited	(72,527)	€ 5.56	(116,181)	€ 4.64	(7,817)	€ 4.64
Exercised	(1,034)	€ 3.54	(891)	€ 2.38	(7,811)	€ 1.78
Expired	—	—	—	—	—	—
Balance at December 31	**3,331,875**	**€ 4.78**	**2,205,989**	**€ 4.88**	**1,108,935**	**€ 4.19**
Exercisable at December 31	1,148,893		615,246		339,352	

The options outstanding at December 31, 2017 had an exercise price in the range of € 1.11 to € 20.34 (2016: € 1.11 to € 20.34, 2015: € 1.11 to € 20.34) and a weighted-average contractual life of 7.9 years (2016: 8.3 years, 2015: 8.3 years).

The weighted-average share price at the date of exercise for share options exercised in 2017 was € 4.32 (2016: € 4.23, 2015: € 19.30).

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

13. Non-current liabilities

(a) Borrowings

	December 31, 2017	December 31, 2016
	(€ in thousands)	
Innovation credit	4,899	4,598
Accrued interest on innovation credit	1,683	1,099
Convertible loans	662	—
Total borrowings	**7,244**	**5,697**
Current portion	(1,960)	—
	5,284	**5,697**

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 2017. 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.

Convertible loans

Convertible loans were issued to Amylon Therapeutics B.V. in 2017 and are interest-bearing at an average rate of 8% per annum. They are convertible into a variable number of ordinary shares within 36 months at the option of the holder or the Company in case financing criteria are met. Any unconverted loans become payable on demand after 24 months in equal quarterly terms.

14. Current Liabilities

	December 31, 2017	December 31, 2016
	(€ in thousands)	
Borrowings	1,960	—
Trade payables	546	328
Social securities and other taxes	1,019	312
Pension premiums	—	13
Deferred income	347	—
Accrued expenses and other liabilities	4,622	6,057
	8,494	**6,710**

At December 31, 2017, current liabilities included deferred income resulting from installments received of the € 6 million grant (ProQR: € 4.6 million) from the European Commission (EC) under the Horizon 2020 program to finance the clinical development of eluforsen.

15. Other income

	2017	2016	2015
	(€ in thousands)		
Grant income	870	1,632	3,188
Rental income from property subleases	625	196	47
	1,495	**1,828**	**3,235**

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 (€ 2.5 million) to support the clinical development of eluforsen. 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: € 4.6 million) to support the clinical development of eluforsen 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 € 31,153,000 in 2017 (2016: € 31,923,000, 2015: € 23,401,000) 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

	2017	2016	2015
	(€ in thousands)		
Wages and salaries	11,855	10,184	7,128
Social security costs	1,285	1,093	596
Pension costs — defined contribution plans	860	764	478
Equity-settled share based payments	4,024	2,454	1,212
	18,024	**14,495**	**9,414**
Average number of employees for the period	139.9	133.4	86.1

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

	December 31, 2017	December 31, 2016	December 31, 2015
Research and Development	96.2	100.4	72.4
General and Administrative	34.0	32.9	27.1
Total number of employees at December 31 (converted to FTE)	**130.2**	**133.3**	**99.5**

Of all employees 125.2 FTE are employed in the Netherlands (2016: 128.3 FTE).

Included in the wages and salaries for 2017 is a credit of € 723,000 (2016: € 807,000, 2015: € 372,000) with respect to WBSO subsidies.

18. Financial Income and Expense

	2017	2016	2015
	(€ in thousands)		
Interest income:			
Current accounts and deposits	90	270	501
Interest costs:			
Interest on loans and borrowings	(596)	(538)	(395)
Foreign exchange result:			
Net foreign exchange benefit/(loss)	(2,669)	738	6,065
	(3,175)	**470**	**6,171**

19. Income Taxes

The calculation of the tax charge is as follows:

	2017	2016	2015
	(€ in thousands)		
Income tax based on domestic rate	10,918	9,776	5,208
Tax effect of:			
Non-deductible expenses	(634)	(622)	(309)
Tax incentives	—	(46)	136
Current year losses for which no deferred tax asset was recognized	(10,257)	(9,045)	(5,035)
Change in unrecognized deductible temporary differences	(25)	(63)	—
Income tax charge	2	—	—
Effective tax rate	— %	— %	— %

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, 2017, the Company has a total amount of € 123.9 million (2016: € 82.9 million, 2015: € 46.9 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.

	2017	2016	2015
Result attributable to equity holders of the Company (€ in thousands)	(43,637)	(39,103)	(20,832)
Weighted average number of shares outstanding	25,374,807	23,346,507	23,343,262
Basic (and diluted) earnings per share (€ per share)	**€ (1.72)**	**€ (1.67)**	**€ (0.89)**

(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 entered into rental agreements for laboratory space and offices.

The lease expenditure charged to the income statement in 2017 amounts to € 2,103,000 (2016: € 1,849,000, 2015: € 703,000). The future aggregate minimum lease payments under non-cancellable operating leases are as follows:

	December 31, 2017	December 31, 2016	December 31, 2015
		(€ in thousands)	
Less than 1 year	1,607	1,775	1,938
Between 1 and 5 years	3,312	5,508	7,212
More than 5 years	—	—	—
Total	**4,919**	**7,283**	**9,150**

The Company leased out a part of its offices in the U.S. and the Netherlands. In 2017, total sublease income amounted to € 625,000 (2016: € 196,000, 2015: €47,000), which is recorded in other income. At 31 December, the future minimum lease payments under non-cancellable leases are receivable as follows:

	December 31, 2017	December 31, 2016	December 31, 2015
		(€ in thousands)	
Less than 1 year	174	463	185
Between 1 and 5 years	—	—	—
More than 5 years	—	—	—
Total	**174**	**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 agreements

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 (€ 584,000) 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 (€ 8,000) 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, Inserm Transfert and Assistance-Publique-Hôpiteaux de Paris, 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 agreements

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 (€ 2.5 million) to support the clinical development of eluforsen.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to CFFT of up to approximately $ 16 million (€ 13 million), payable in three equal annual installments following the first commercial sale of eluforsen, 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 (€ 2.5 million) if net sales of eluforsen exceed $ 500 million (€ 417 million) in a calendar year. Lastly, the Company is obligated to make a payment to CFFT of up to approximately $ 6 million (€ 5 million) if it transfers, sells or licenses eluforsen other than for certain clinical or development purposes, or if the Company enters into a change of control transaction prior to commercialization. However, the payment in the previous sentence may be set-off against the $ 16 million milestone payment. 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.

On February 9, 2018, the Company entered into an agreement with Foundation Fighting Blindness (FFB), under which FFB will provide funding of $7.5 million (€ 6.3 million) to advance QR-421a into the clinic and will receive future milestone payments.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to FFB of up to approximately $ 37.5 million (€ 31.3 million), payable in four equal annual installments following the first commercial sale of QR-421a, the first of which is due within 60 days following the first commercial sale. The Company is also obligated to make a payment to FFB of up to approximately $ 15 million (€ 12.5 million) if it transfers, sells or licenses QR-421a other than for certain clinical or development purposes, or if the Company enters into a change of control transaction. However, the payment in the previous sentence may be set-off against the $ 37.5 million milestone payment. Either FFB 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 € 7,704,000 at December 31, 2017 (2016: € 8,856,000). Of these obligations an amount of € 6,094,000 is due in 2018, 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

The remuneration of the supervisory board members in 2017 is set out in the table below:

	2017			
	Short term employee benefits	Post-employment benefits	Share-based payment	Total
	(€ in thousands)			
Mr. Dinko Valerio	36	—	87	123
Mr. Henri Termeer	28	—	160	188
Mr. Antoine Papiernik	76	—	—	76
Ms. Alison Lawton	31	—	99	130
Mr. Paul Baart	84	—	—	84
Mr. James Shannon	33	—	92	125
	288	—	**438**	**726**

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
	(€ in thousands)			
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 2015 remuneration 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**

As at December 31, 2017:

- Mr. Valerio holds 1,043,420 ordinary shares in the Company, as well as 88,425 options. These options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant. In 2016, Mr. Valerio was granted 23,989 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 6.08 per option. In 2017, Mr. Valerio was granted 32,164 options at an average exercise price of € 4.65 per option.

  On September 12, 2017, Mr. Valerio provided a convertible loan to Amylon Therapeutics B.V. This loan is interest-bearing at an average rate of 8% per annum and is convertible into a variable number of ordinary shares within 36 months at the option of the holder or the Company in case financing criteria are met. Any unconverted loans become payable on demand after 24 months in equal quarterly terms.

- Mr. Termeer passed away on May 12, 2017. His full board fee was awarded post mortem.

- 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 3,625,925 ordinary shares, Mr. Papiernik may be deemed to have share voting and investment power with respect to such shares.

- Ms. Lawton holds 68,973 options. In 2015, Ms. Lawton was granted 4,970 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 16.10 per option. In 2016, she was granted 23,989 options with an exercise price of € 6.08 per option. In 2017, she was granted 32,164 options with an average exercise price of € 4.65 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 61,538 ordinary shares in the Company and 65,233 options. In 2016, he was granted 33,069 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 4.32 per option. In 2017, he was granted 32,164 options at an exercise price of € 4.65 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

Our management board is supported by our officers, or senior management. The total remuneration of the management board and senior management in 2017 amounted to € 5,096,000 with the details set out in the table below:

	2017			
	Short term employee benefits	**Post employment benefits**	**Share-based payment**	**Total**
	(€ in thousands)			
Mr. D.A. de Boer[1]	570	8	622	1,200
Mr. R.K. Beukema[2]	411	15	261	687
Management Board	981	23	883	1,887
Senior Management	1,719	66	1,424	3,209
	2,700	**89**	**2,307**	**5,096**

1 Short term employee benefits includes a bonus for Mr. Daniel de Boer, of € 217,000 based on goals realised in 2017.
2 Short term employee benefits includes a bonus for Mr. René Beukema, of € 113,000 based on goals realised in 2017.

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[1]	429	7	391	827
Mr. R.K. Beukema[2]	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 includes a bonus for Mr. Daniel de Boer of € 131,000 based on goals realised in 2016.
2 Short term employee benefits 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[1]	397	7	164	568
Mr. R.K. Beukema[2]	313	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.

As at December 31, 2017:

- Mr. de Boer holds 1,152,293 ordinary shares in the Company as well as 449,338 options. In 2015, Mr. de Boer was awarded a total number of 23,902 options to acquire ordinary shares at € 16.10 per option. In 2016, he was awarded 129,727 options at an exercise price of € 6.64 per option. In 2017, he was awarded 239,717 options at an exercise price of € 4.65 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 8.3 years at December 31, 2017.

- Mr. Beukema holds 346,239 ordinary shares in the Company as well as 299,081 options. In 2015, Mr. Beukema was awarded 8,713 options to acquire ordinary shares at € 16.10 per option. In 2016, he was awarded 50,608 options at an exercise price of € 6.64 per option. In 2017, he was awarded 101,408 options at an exercise price of € 4.65 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 7.3 years at December 31, 2017.

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:

	2017	2016	2015
	(€ in thousands)		
Audit fees	175	165	193
Audit-related fees	140	39	—
Tax fees	—	—	—
All other fees	—	—	—
	315	**204**	**193**

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.

25. Subsequent events

In January 2018, ProQR announced a research collaboration with Galapagos, where the Company's Axiomer technology will be applied to certain fibrosis targets identified by Galapagos. The Axiomer platform may be applicable to more than 20,000 disease-causing mutations. The Company plans to develop its Axiomer platform in select therapeutic areas and continue to validate and create value for this novel technology through licensing, partnering and other strategic relationships.

In February 2018, the Company entered into a partnership with Foundation Fighting Blindness in which ProQR will receive up to $7.5 million (€6.3 million) in funding from FFB for the pre-clinical and clinical development of QR-421a for Usher syndrome type 2A targeting mutations in exon 13.

ARTICLES OF ASSOCIATION OF:

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

as per 27 February 2018.

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 27 February 2018 before a deputy of P.C. Cramer-de Jong, civil law notary in Amsterdam, the Netherlands.

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.

ARTICLES OF ASSOCIATION
DEFINITIONS AND INTERPRETATION
Article 1

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 organizationally 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

Article 2

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

2.2 The Company has its corporate seat in Leiden.

OBJECTS

Article 3

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

Article 4

4.1 The Company's authorised share capital amounts to seven million two hundred thousand euro (EUR 7,200,000).

4.2 The authorised share capital is divided into:

a. ninety million (90,000,000) ordinary shares; and

b. ninety million (90,000,000) 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

Article 5

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

Article 6

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

Article 7

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

Article 8

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

Article 9

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

Article 10

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

Article 11

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 - TRANSFER REQUIREMENTS

Article 12

12.1 Except as otherwise provided or allowed by Dutch law, the transfer of a share shall require a deed to that effect 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

Article 13

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

Article 14

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

Article 15

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

Article 16

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

Article 17

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

Article 18

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

Article 19

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

Article 20

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

Article 21

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

Article 22

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

Article 23

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

Article 25

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

Article 26

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

Article 27

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

Article 28

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

Article 29

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

Article 30

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 **Error! Reference source not found.**, 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

Article 31

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

Article 32

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

Article 33

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 Article 34**

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

Article 35

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

Article 36

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.

CONFIDENTIAL

LICENSE AGREEMENT

N° *09533C10*

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.

This License Agreement (the "**Agreement**") is made as of its last date of signature by all signatories (the "**Effective Date**") by and between:

Inserm Transfert SA, a limited company (*société anonyme à directoire et conseil de surveillance*) organized under the laws of France, with share capital of €9,573,470, whose registered headquarters are located at 7 rue Watt, 75013 Paris, France, SIRET No. 434 033 619 00025 business (APE) code 7219Z, Paris Trade and Companies Registry No. B 434 033 619, represented by its Chairman of the Management Board, Mrs. Pascale Augé,

Acting as delegate of the French National Institute of Health and Medical Research (Institut National de la Santé et de la Recherche Médicale – hereinafter "**Inserm**"), a public scientific and technological institute, having its registered headquarters at 101 rue de Tolbiac, 75013 Paris, France.

Acting on behalf of Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), Genethon and École Nationale supérieure de physique et de chimie industrielles de la ville de Paris (ENSCP) according to a mandate allowing Inserm Transfert to execute the Agreement on their behalf.

Hereinafter referred to as "**Inserm Transfert**"

And

Assistance-Publique-Hôpitaux de Paris, located 3 avenue Victoria, 75184 Paris Cedex 04, France, represented by its Managing Director, Mr Martin Hirsch, Represented by: Mrs Florence Favrel-Feuillade, Director of the Department of Clinical Research and Innovation, Carré Historique de l'Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris in accordance with delegation, authorising her to sign the present contract,

Hereinafter referred to as "**AP-HP**"

on the one hand

And

ProQR Therapeutics IV B.V., a private company with limited liability organized under the laws of Netherlands, whose registered headquarters are located at Zernikedreef 9, 2333CK Leiden, the Netherlands, represented by its CEO, Daniel de Boer,

Hereinafter referred to as "**Licensee**",

on the other hand.

Inserm Transfert, Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris, Généthon and AP-HP and Licensee are hereinafter referred to collectively as the "**Parties**" and individually as a "**Party**".

BACKGROUND

A. The team of Jean-Michel Rozet ("Laboratory") in Inserm's research laboratory U781 (today U1163), which was under the joint supervision of Inserm and Université Paris Descartes and a team in Inserm's research laboratory U1022 which is under the joint supervision of Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris have made an invention relating to Exon skipping therapy for Leber's congenital amaurosis ("LCA"). This invention is the subject of a priority patent application No EP 11305735 (IT reference BIO09533), filed on June 10, 2011, which was continued as an international patent application PCT/EP2012/060906, filed on June 8, 2012 (WO/2012/168435), and which was subsequently prosecuted in Europe (EP 12729421.3) and the United States of America (US 9,012,425; US 9,487,782 ; US 9,777,272 and US15/692,669) and co-owned by Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris, Généthon and AP-HP. Université d'Evry Val d'Essone was also designated as co-applicant of all or part of the aforementioned patent applications/patents and Inserm Transfert is, at the Effective Date, in the process of obtaining the assignment to Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris, Généthon and AP-HP of Université d'Evry Val-d'Essone's share in the above mentioned patent applications/patents.

B. Inserm Transfert is Inserm's private law wholly-owned technology transfer subsidiary, created by a French decree dated June 6, 2000. Effective January 1, 2006, Inserm delegated to Inserm Transfert the management of its technology transfer activities resulting from the French decree No 83-975 relating to Inserm's organization and functioning. As of January 1, 2006, Inserm Transfert is notably in charge of the management of patents, know-how, materials and other technologies owned or co-owned by Inserm including the negotiation, signature and management of license related thereto.

It is however specified that this delegation does not entail the transfer to Inserm Transfert of the property rights held or jointly held by Inserm.

For the performance of this agreement, Inserm is not considered as a third party.

C. Licensee wishes to obtain a license on the above mentioned patent application(s) for the development and commercialization of therapeutic oligonucleotides for the prevention and treatment of Leber congenital amaurosis.

NOW, THEREFORE, in consideration of the mutual covenants, conditions and undertakings herein contained, the Parties agree as follows:

PRELIMINARY ARTICLE
DEFINITIONS

As used in the present agreement, the following terms shall have the meanings indicated:

"Agreement" shall mean the full present license agreement including its potential amendments and appendices.

"Affiliate" shall mean any commercial capital or partnership company, which via a share to the capital or any other means controls Licensee, is controlled by Licensee, or is under common control with Licensee. For the purpose of this definition, control means the ownership of more than fifty percent (50%) of the voting rights or of the rights to direct the management and policies of an entity.

The following relationships between legal entities shall not in themselves be deemed to constitute controlling relationships:

(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates; or

(b) the legal entities concerned are owned or supervised by the same public body.

The rights granted to the Affiliates under the terms of this Agreement only apply to entities qualifying as Affiliate at the time the rights are exercised. If, during the term of the Agreement, an entity were to lose the qualification of Affiliate, the rights acquired by this entity as Affiliate of Licensee will automatically terminate, unless written consent of Inserm Transfert is given.

This entity will however remain subject to any obligation under the Agreement that shall by nature remain in force, in particular obligations relating to Confidential Information. Notwithstanding the above, Licensee shall remain liable for the ongoing performance of the obligations under this Agreement by its Affiliates.

"Co-Owners" shall mean Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris, Généthon and AP-HP.

"Development Activities" shall mean all activities and studies to be conducted directly by Licensee, or by a third party or Affiliate on behalf of Licensee or by Sublicensee, in accordance with the development plan handed to Inserm Transfert as provided under 3.1, including activities and studies required for the development and commercialization of Products, either directly by Licensee or indirectly through its Affiliates and/or Sublicensees.

"Effective Date" shall mean the last date of signature by the last signatory.

"Field" shall mean the prevention and treatment of Leber congenital amaurosis.

"Improvements" shall mean any improvement, whether patentable or not, which may not be practiced without reproducing at least one claim of the Patent Rights or which use is legally dependent upon the Patent Rights, in the meaning of intellectual property laws.

"Net Sales" shall mean the total amount invoiced (excluding taxes) to, third parties, including distributors, on sales or other mode of transfer of the Products in all its forms by Licensee and/or its Affiliates and/or its (their) Sublicensee(s) less any:

(a) reimbursement in respect of returned Products within the limit of the sale's price of said Products,
(b) taxes or other customs duties relating to the Products and borne by Licensee,
(c) costs of transportation, shipping, handling and insurance and
(d) normal trade discounts, if not already deducted of the sale's price.

It is understood that the deductions under (c) and (d) shall not altogether exceed the maximum level of **** of the total amount invoiced for all countries in the Territory during the applicable year.

Net Sales of Licensee shall not include intermediate sales between Licensee and its Affiliates and/or its (their) Sublicensee(s) and/or their Affiliates or sales between their Affiliates; for resale of Products, as the case may be, Net Sales shall include the amounts invoiced to third parties on the resale.

Net Sales shall only include the sales between the Licensee and/or its Affiliates and/or its (their) Sublicensee(s), on the one hand, and third parties, on the other hand.

Net Sales shall also include the fair market value of any non-cash consideration received by Licensee and/or its Affiliates and/or its (their) Sublicensee(s) for the sales or other modes of transfer of Products.

If a Product is sold in a kit in combination or in association with other products that are not Products (it being specified, for clarity, that the definition of Products also includes Non Dissociable Products as defined below) and that are sold separately by Licensee for other applications not related to the use of Products, Net Sales shall be calculated by multiplying net sales of the kit or association by the fraction A/(A+B), where A is the total catalogue price of the Products during the applicable year in the country in which the sale was offered if sold

separately and B is the total of the catalogue prices of all other products in the kit or association during the applicable year in said country if sold separately. In case no separate list or catalogue prices are available for said products, Licensee shall reasonably determine the values of B on the basis of catalogue or list prices for comparable products.

In the case of non dissociable technologies, Net Sales shall cover the sales of the Non Dissociable Products according to the definition of Products below.

"Patent Rights" shall mean EP 11305735 (IT reference BIO 09533), filed on June 10, 2011, co-owned by Inserm, Université Paris Descartes, Centre National de la Recherche Scientifique (CNRS), École Nationale supérieure de physique et de chimie industrielles de la ville de Paris, Généthon and AP-HP**,** titled "METHODS FOR THE TREATMENT OF LEBER CONGENITAL AMAUROSIS" and quoting notably Jean-Michel Rozet, J. Kaplan, X. Gérard, A. Kichler, D. Scherman, I. Perrault and A. Munnich as inventors and any subsequent patent application(s) corresponding thereto, including any international applications, divisional applications, continuations, continuations in part, re-examination applications or national stage applications, and each patent that issues or reissues from any of these patent applications. For the avoidance of doubt, Patent Rights include supplementary protection certificates ("**SPCs**") and other extension(s) of similar nature but do not include any improvements made by INSERM or the Co-Owners.

"Product(s)" shall mean:

(i) any product, composition, method or process the manufacture, use or sale of which would constitute, but for the license granted herein, an infringement of the Patent Rights and/or which include and/or are developed and/or manufactured using the invention subject of the Patent Rights. Products shall be deemed to include the performance of services in the Field and/or any product, composition, method, process or service which would constitute, but for the license granted herein, an infringement of the Patent Rights and/or using the invention subject of the Patent Rights,

(ii) As well as:

(any product, composition, method, process or service that cannot be dissociated from product, composition, method, process or service defined in (i), from a commercial point of view or from a regulatory point of view (the "**Non Dissociable Products**"). For the purpose of the present definition, two elements are non dissociable from a commercial point of view when said non dissociable products are not offered for sale separately under a distinct price reflecting their own added value. For the purpose of the present definition, two elements are non dissociable from a regulatory point of view when they are statutorily required to be registered and sold as a one and only item (such as therapeutic combinations, drug delivery device).

"Sublicensee" shall mean any non-Affiliate third party to whom Licensee, Sublicensee or multiple tiers sublicensees grants a sublicense (or an option) for the development, manufacture, use and commercialization of Products in all or part of the Field and Territory.

"Territory" shall mean the world.

Words indicating the singular may be interpreted to be the plural and vice-versa.

1.
NATURE, OBJECT AND SCOPE OF THE LICENSE

1.1. Inserm Transfert and the Co-Owners hereby grant to Licensee an exclusive, royalty-bearing license under the Patent Rights to develop, have developed, make, have made, use, have used and sell, have sold or otherwise distribute Products within the Field and in the Territory.

1.2. Under the license granted under Article 1.1, Licensee may grant sublicenses (including the right to grant multiple tiers sublicenses subject to the following provisions), which sublicenses shall not contain any provision which would cause it to extend beyond the scope of this Agreement.

Licensee shall provide Inserm Transfert notification of the identity and address of the proposed Sublicensee and a summary of terms of the sublicense (whatever its tier) within thirty (30) days for prior written approval by Inserm Transfert; it being specified that Inserm Transfert may only disagree to the granting of the sublicense for one of the following reasons:

(i) Sublicensee's activities conflict with the public order/ethical obligations of the Co-Owners and/or Inserm Transfert (e.g. affiliations with Tobacco, Guns (legal firms), firms who are recognized by the public harm the human health, entity funded through or by organized crime) or,

(ii) If the sublicense tarnishes the Co-Owners and/or Inserm Transfert's image (e.g. affiliations with Tobacco, Guns (legal firms), firms who are recognized by the public harm the human health, entity funded through or by organized crime) or

(iii) If the Co-Owners and/or Inserm Transfert are currently involved or have been involved in a litigation with Sublicensee within the three (3) years prior to the sublicense notification from Licensee and can provide written evidence of such litigation, or

(iv) If the sublicense implies financial conditions which are more favourable to Sublicensee than that granted to Licensee.

Should Inserm Transfert fail to respond within thirty (30) days of receipt of the notification of the proposed sublicense, Inserm Transfert shall be deemed to have approved the sublicense

agreement. A copy of each sublicense agreement shall be provided to Inserm Transfert as soon as it is executed.

Licensee shall remain entirely responsible for the proper performance of the sublicenses and shall be solely responsible towards Inserm Transfert and the Co-Owners for the performance by Sublicensees of all obligations binding upon Licensee under the Agreement. In particular, Licensee undertakes to include in the sublicense agreement confidentiality clauses similar to the one contained herein and not to conclude any sublicense which term would extend beyond the term of the Agreement, without prejudice to termination clauses.

1.3. The Co-Owners reserve the right to practice the Patent Rights in the Field for teaching and/or academic and/or research purposes (including clinical research) , whether by themselves or in collaboration with other academic institutions, including the right to transfer to any academic institution any material and product covered by the Patent Rights, without compromising the exclusive rights granted to Licensee, Affiliates and/or Sublicensees under this and Agreement, and excluding any research carried out in collaboration with or on behalf of a third industrial party. Inserm Transfert and the Co-owners shall not grant any rights of commercial exploitation on the Patents Rights in the Field to any third party.

Outside the Field, the Co-Owners are free to use the Patent Rights for any purpose whatsoever.

2.
TERM

This Agreement is effective as of the Effective Date. Unless terminated earlier pursuant to Article 8, it shall last, on a country-by-country basis, until the last to occur of the following events (i) as of the Effective Date and until the invalidation or expiration of the last to expire or to be invalidated Patent Rights which covers the manufacture, use or sale of the Product in said country or until the expiration of the exclusive commercialization right granted by a regulatory agency to a Product as orphan drug or (ii) as of the Effective Date and for five 5 years after the first commercial sale of a Product in the country in which this product is sold. The Parties have agreed that the effect of the Agreement will continue beyond the lifetime of the Patents in order to take into account the length of the development needed before the marketing of the Products as well as the associated costs for the Licensee and/or its Sublicensees. To that end, the Parties have decided to spread out the global financial compensation due for the rights granted, until and including the marketing of the Products, which generates revenues for the Licensee and/or its Sublicensees; rather than concentrating this financial compensation during the lifetime of the Patents and therefore mostly during the development.

3.
DEVELOPMENT – COMMERCIALIZATION

3.1 The Parties acknowledge that, as at the Effective Date, Licensee has provided Inserm Transfert with a development plan (the "**Development Plan**") which describes the terms under which Licensee intends to conduct the Development Activities, the estimated schedule for performance of said Development Activities as well as the estimated date of first commercial sale of the Products. The Development Plan is attached as Appendix 1, shall form an integral part of the Agreement and shall be updated as the Development Activities progress, as defined below.

3.2 Licensee undertakes to inform Inserm Transfert of any unforeseen event relating to said development work that could in itself delay the development activities by more than nine (9) months. In such cases, Licensee shall provide Inserm Transfert with an updated Development Plan that Inserm-Transfert shall agree on if said delay does not result from financial or strategic decisions (such as internal prioritization of projects) from Licensee and results from an external event beyond Licensee's control and if Licensee provides information as to how it intends to remedy, as much as reasonably possible, the delay and pursue the development and commercialization of a Product and accessibility of a Product to the benefit of the patients.

3.3 Licensee agrees to undertake commercially reasonable efforts to develop a Product as soon as possible, consistent with reasonable business practices and in compliance with the Development Plan, or as updated according to article 3.2 if the case occurs.

3.4 Licensee agrees to undertake commercially reasonable efforts to commercialize a Product as soon as possible, consistent with reasonable business practices and with the regulatory approvals necessary in the Territory.

3.5 Inserm Transfert may terminate the Agreement *ipso jure* in whole or in part in the event Licensee fails to meet its obligations under Articles 3.2 to 3.4 and if Licensee has not remedied its failure in connection therewith within one hundred and twenty (120) days as from a written notice to do so sent by Inserm Transfert.

3.6 More specifically, Inserm Transfert may terminate the Agreement *ipso jure* in whole or in part in any country after a sixty (60) days advance notice (to the exclusion of any other formality), in the following cases:

(i) Licensee and/or its Sublicensees (including multiple tiers Sublicensees) interrupts Development Activities in respect of Products for one (1) year or more; or

(ii) Licensee and/or its Sublicensees (including multiple tiers Sublicensees) interrupts commercialization of Products for more than twelve (12) months after a first commercialization in a country of the Territory, or

(iii) in the absence of commercialization of a Product within two years following the obtaining of its marketing approval in a country of the Territory, or any other equivalent authorization, or

(iv) if Licensee and/or its Sublicensees (including multiple tiers Sublicensees) has not put a Product into commercial use and is not keeping Products reasonably available to the public within twelve (12) years from the Effective Date.

For clarification only a case of *Force Majeure* (as defined under Article 9.8) should be considered as an involuntary interruptions of Development Activities.

3.7 Licensee shall comply with all applicable laws and regulations in connection with its activities pursuant to this Agreement.

3.8 More specifically, Licensee undertakes to use commercially reasonable efforts to obtain the regulatory approvals required prior to the introduction of Products into the commercial market in the countries in which Licensee contemplates to sell the Products.

Licensee shall be responsible (i) for obtaining and maintaining in its own name and at its sole expense, or in the name and at the expense of any person it shall designate, the registrations and marketing authorizations of the Products in the Territory, and (ii) for the compliance with local laws.

3.9 In the context of clinical trials carried out by or on behalf of Licensee, Licensee undertakes to comply with all applicable laws and regulations and, for clinical trials conducted in France, to comply with the provisions of the French Public Health Code as to the protection of persons involved in biomedical research. Licensee shall guarantee and hold harmless each of Inserm Transfert and the Co-Owners of any action initiated by a third party in the context of such trials.

3.10 Licensee shall be free to conduct its promotion, manufacturing and distribution policy, provided it has obtained the prior approval of the Co-Owners and Inserm Transfert for any use of their names, pursuant to Article 7.6.

3.11 Licensee shall keep Inserm Transfert regularly informed of the Development Activities' progress. To that end, Licensee shall provide Inserm Transfert, within sixty (60) days from December 31 of each calendar year, with a written annual report with a summary of the progress of its Products development as well as the commercialization efforts, in compliance with the Development Plan. Such progress reports shall include, among other things, the following topics: summary of work completed, summary of work in progress, updated schedule of anticipated milestones achievements and regulatory approvals, manufacturing and sublicensing efforts and commercialization plan for the launch of the Products. In case of termination of this Agreement, Licensee shall provide Inserm Transfert with a last progress report, within sixty (60) days following termination.

4.
FINANCIAL CONDITIONS AND REPORTS

4.1 In consideration for the license rights granted under the Agreement, Licensee undertakes:

- to exercise commercially reasonable efforts to engage the necessary funds for the proper performance of the Development Activities, it being specified that it is for Licensee to define the means to be allocated to the Development Activities, and

- to be in charge for the payment of all patent expenses related to the Patent Rights incurred prior to and after the Effective Date, as detailed under the Agreement, and

- to pay Inserm Transfert royalties on direct and indirect exploitation of the licensed technology, as well as milestone payments.

4.2 Patent Expenses.

For purposes of this Article 4.2 "filing, prosecution, extension, maintenance and defense of patents" shall be deemed to include, without limitation, the preparation and filing of applications, granting, examination, conduct of interferences and/or oppositions and/or requests for re-examinations, validations, reissues, addition certificates, continuations, continuations in part of patents.

The out-of-pocket expenses relating to the filing, prosecution, extension, maintenance and defense of the Patent Rights are hereafter referred to as "**IP Costs**".

Licensee reimburses all IP Costs incurred by the Co-Owners and/or Inserm Transfert prior to the Effective Date (the "**Past IP Costs**"), which reimbursement is demandable and due as at the Effective Date.

Inserm Transfert shall provide a summary statement of the Past IP Costs within two (2) months from the Effective Date, together with justifying documentation related thereto. Licensee shall reimburse such Past IP Costs within thirty (30) days of receipt of an invoice by Inserm Transfert for a maximum of ****

As of the Effective Date, Licensee shall be in charge of all IP Costs, in France and abroad, and Inserm Transfert shall instruct the patent agent(s) in charge of the Patent Rights or the company in charge of managing annual maintenance fees for the Patent Rights, to directly invoice Licensee for said IP Costs.

IP Costs due from the Licensee pursuant to the Agreement are neither reimbursable nor creditable against any other payment due under the Agreement.

4.3 Lump sum payments.

4.3.1. Milestone Payments. In partial consideration of the rights and license granted by Inserm Transfert to Licensee herunder, Licensee agrees to make the following payments to Inserm Transfert upon the completion of the milestone event specified below by Licensee and/or its Sublicensee(s) and/or its (their) Affiliates and/or by a subcontractor on behalf of Licensee and/or its Sublicensee(s) and/or its (their) Affiliates:

MILESTONE	AMOUNT (excl. taxes)
Completion of a clinical trial more advanced than the First in Man for a first Product	****€ (**** euros)
First marketing authorization or any foreign equivalent for a first Product	****€ (**** euros)

Notwithstanding Article 3.11, Licensee shall notify Inserm Transfert in writing of the occurrence of the above milestone within thirty (30) days of its occurrence. It is understood and agreed that the amounts specified under this Article 4.3 shall be payable within thirty (30) days after sending of a corresponding invoice by Inserm Transfert.

4.4 Exploitation Royalties.

4.4.1 Royalties on Net Sales

In further consideration of the rights and license granted under this Agreement, Licensee shall pay to Inserm Transfert a running royalty on Net Sales of Products, by Licensee and/or its Sublicensee(s) and/or its (their) Affiliates in the Territory according to the following royalty rates:

- **** (****%) of Net Sales for the part of aggregate annual Net Sales in the European Union (i.e. including all indications) during applicable year which are below **** Euros (**** €), and.

- **** (****%) of Net Sales for the part of aggregate annual Net Sales in the European Union (i.e. including all indications) during applicable year which are above **** euros (**** €) and below **** Euros (**** €), and

- **** (****%) of Net Sales for the part of aggregate annual Net Sales in the European Union (i.e. including all indications) during applicable year which are above **** euros (**** €)

- **** (****%) of Net Sales for the part of aggregate Net Sales outside the European Union (i.e. including all indications) during applicable year

If (i) a Product is not covered by at least one claim of a pending or issued Patent Rights (which has not been definitively held invalid) in the country of the Territory where it is sold, and (ii) there is no exclusive commercialization right granted by a regulatory agency to such Product as orphan drug, then the royalty rate mentioned under 4.4.1 above will be reduced by **** for the part of Net Sales of such Product made in said country.

Notwithstanding all deductions provided for under the Agreement, the royalty rate on Net Sales of Products by Licensee or its Sublicensee(s) or its (their) Affiliates during the applicable calendar year shall not be less than **** (**** %) of Net Sales of Products.

If a Product is not covered by at least one claim of a pending or issued Patent Rights (which has not been definitively held invalid (with no appeal possible) in the country of the Territory where it is sold and (i) if Licensee's, Licensee's Affiliates, Sublicensee's, Sublicensee's Affiliates aggregate total Net Sales of said Product in said country of the Territory have been reduced by more than **** percent (****%) compare to the preceding applicable year and (ii) such reduction is only attributable to the presence of a generic product of said Product marketed by a third industrial company on said country of the Territory, then no royalty on Net Sales of said Product in said country of the Territory shall be due by Licensee for the applicable year. The burden of proof of establishing that such reduction is only attributable to the marketing of a generic product lies on Licensee.

4.5 Payments

4.5.1 Licensee shall provide Inserm Transfert with annual written revenue reports ("**Revenue Reports**") by 31 March of each calendar year, which Revenue Reports shall be certified as true and accurate by an independent auditor. Such reports shall include, for the preceding calendar year:

- a reference to the present Agreement,
- the number, description, and aggregate Net Sales for each Product,
- the total amount and description of applicable deductions pursuant to the Net Sales definition,
- the number, description, and aggregate sales of Products by Sublicensee (including multiple tiers Sublicensees) and of Sublicense Revenues for each Product,
- revenues arising from assignment/transfer of the Agreement,
- royalty rates applied,
- detailed total amount due to Inserm Transfert.

The payments due for the applicable calendar year shall be made within thirty (30) days following issuance of a corresponding invoice by Inserm Transfert after acceptance of the Revenue Report. Payments shall be made with reference to the invoice number and

shall be paid by bank wire transfer to:

Inserm Transfert SA, Recette Générale Finances Paris, 94 rue de Réaumur, 75104 Paris Cedex 02, France

Bank Code: ****

4.5.2 In case of termination or expiration of the Agreement, Licensee shall provide Inserm Transfert with a final Revenue Report within thirty (30) days following termination or expiration of the Agreement.

4.5.3 The above-mentioned amounts will be increased by VAT at the rate in force on the date of the triggering event.

4.5.4 Any payments due which are not paid on the date such payments are due under this Agreement shall bear interest at the rate of three times the legal interest rate in force at the issuance date of the invoice, without prejudice to Inserm Transfert's right to terminate the Agreement. Late payment penalties will be invoiced separately.

4.5.5 All payments under the Agreement shall be due by Licensee and (i) are non-refundable and non-creditable against any payment hereunder (even in case of early termination) and shall be irrevocably retained by Inserm Transfert, (ii) are due whether the development of the Product is performed by Licensee and/or its Affiliates and/or by a subcontractor on behalf of Licensee and/or its Affiliates and (iii) are due whether the Patent Rights are issued or not. All payments still outstanding at the expiration or termination of this Agreement shall be made by Licensee to Inserm Transfert within thirty (30) days thereof.

4.6 Records; Inspection.

4.6.1 Licensee shall keep and shall cause its Affiliates and Sublicensees to keep specific books of account and records for the purpose of precisely evaluating commercial transactions and of controlling the sums payable to Inserm Transfert under this Agreement. Such books and records shall be kept accessible to Inserm Transfert for at least three (3) years following the provision of the Revenue Report related thereto.

4.6.2 Such books and records will be available for inspection during such three (3) year period by a representative of Inserm Transfert or an independent auditor appointed by Inserm Transfert. Inserm Transfert shall bear the costs and expenses of such inspections, unless a variation or error producing an underpayment in sums payable exceeding **** of the amount paid for the period covered by the inspection is established in the course of any such inspection, in which case, the costs and expenses of such inspection shall be borne by Licensee. Any unpaid amounts that are discovered will be paid by Licensee, together with interest on such unpaid amounts at the rate specified in Article 4.5.4 above.

5.
PATENTS - INFRINGEMENT

5.1 As of the Effective Date and for as long as this Agreement is effective, Licensee shall manage the filing, prosecution, extension, maintenance and defense of the Patent Rights in the Territory, at its own cost; provided however that Licensee shall notify Inserm Transfert before taking any substantive actions with respect to (i) the choice of proceedings and the scope and content of all patent applications within the Patent Rights; and (ii) content or proposed responses to official actions of national patent offices regarding the prosecution of the Patent Rights, and shall give Inserm Transfert a reasonable opportunity to comment in respect to items (i) and (ii) and shall reasonably consider any comments received from Inserm Transfert. For purposes of this Article 5, "filing, prosecution, extension, maintenance and defense of patents" shall be deemed to include, without limitation, the preparation and filing of applications, granting, examination, conduct of interferences and/or oppositions and/or requests for re-examinations, validations, reissues, addition certificates, continuations, continuations in part of patents.

If Licensee elects not to maintain Patent Rights or not to pursue the filing, prosecution, extension, maintenance and defense of the Patent Rights in a country, Licensee shall promptly notify Inserm Transfert of such election, but in no case later than sixty (60) days prior to any required action relating to the filing, prosecution, extension, maintenance and defense of the Patent Rights. In such event, Inserm Transfert may at its sole discretion, decide to continue the filing, prosecution, extension, maintenance and defense of such patent application or patent in the name of the Co-Owners and at their expense, in such country, whether in France or abroad.

In such a case, Licensee may, at Inserm Transfert's discretion, have no further right or license thereunder in the concerned countries and/or Patent Rights and Licensee will not be under the obligation to pay any IP Costs for the patent applications or patents concerned. The definition of Patent Rights and/or Territory may be revised accordingly by Inserm Transfert, at its discretion.

In any case, only the Co-Owners may file for a Supplementary Protection Certificate (SPC), at Licensee's cost, and the Co-Owners agree to do so at the request of the Licensee only if this request does not harm with obtaining the SPC. To that end, Licensee undertakes to inform Inserm Transfert of the grant of a marketing authorization (MA) within one (1) month of such grant and to provide Inserm Transfert with a copy of such MA. The Co-Owners shall then file the SPC application within two (2) months of receipt of the copy of the MA.

5.2 Licensee shall act to the best of the Co-Owners, Inserm Transfert and inventors' interest in the frame of any action necessary to enforce the Patent Rights, and in particular in the case of an infringement action against a third party infringer or initiated against Licensee.

5.3 If Inserm Transfert or Licensee comes to believe in good faith that Patent Rights are being infringed by a third party, the Party first having knowledge of such infringement shall promptly notify the other. In any such case, the Parties shall discuss how best to proceed.

If an action is necessary and efficient, the Co-Owners shall have the right, but no obligation, to bring any legal action in their name and at their own expense. The Co-Owners shall retain all damages and costs recovered in connection therewith. In such a case, Licensee will nevertheless retain the right, if applicable, to join any such action initiated by the Co-Owners at its own expense to obtain indemnification for damages which Licensee alone have incurred.

Should Inserm Transfert and the Co-Owners decide not to bring an infringement action and if Licensee is the sole licensee on the Patent Rights, Licensee shall have the right, but no obligation, to prosecute at its own expense any action against third party infringement of the Patent Rights, absent any response or action formulated by Inserm Transfert and/or the Co-Owners within thirty (30) days of its absent any response or action formulated by Inserm Transfert and/or the Co-Owners within thirty (30) days of its after written notice to Inserm Transfert of its intention to do so.

The license granted pursuant to this Agreement expressly includes the rights for Licensee to defend any actions against the Patent Rights, such as action to declare the Patent Rights invalid or non-infringed, the right to sue for infringement of the Patent Rights and/or the right to recover any applicable damages resulting from infringement of the Patent Rights and to pursue any other remedies available, including injunctions, in accordance with article 5.3.

The Parties shall provide each other with the documents and elements necessary to the conduct of the above mentioned actions.

Licensee shall keep Inserm Transfert reasonably appraised of all developments in any action, and will seek the prior approval of Inserm Transfert on any substantive submissions or positions taken in the litigation that might affect the scope, validity or enforceability of the Patent Rights.

If an action initiated by Licensee obliges the Co-Owners to take part in an invalidity action or counterclaim for invalidity of the Patent Rights, Licensee shall pay all the legal costs and expenses, including attorney’s fees, incurred by Inserm Transfert and/or the Co-Owners.

Licensee will not sign with the defendant any settlement or agreement which would limit the scope of the Patent Rights without the prior written approval of Inserm Transfert, which may not be unreasonably delayed or withheld.

Damages and sums received by Licensee in the frame of infringement actions shall be, after deduction of the proceedings costs, considered as Net Sales and subject to the applicable royalty payments.

The Co-Owners shall in any event have the right, but no obligation, to join in the action initiated by Licensee.

5.4 Should an infringement action be brought against Licensee as a result of the exploitation of the Patent Rights, Licensee may not claim any compensation to Inserm Transfert and/or the Co-Owners, nor any reimbursement of the sums paid, nor any reductions of the sums due under Article 4 at the time of the final court decision.

6.
WARRANTIES – INDEMNIFICATION - INSURANCE

6.1 a) Inserm Transfert and the Co-Owners declare and warrant (i) the material existence of the Patent Rights as at the Effective Date, (ii) that they have the rights to grant licenses in respect of the Patent Rights. Inserm Transfert and the Co-Owners do not offer any other warranties of any kind, express or implied.

b) Inserm Transfert guarantees Licensee against any and all claims from Université d'Evry Val d'Essone whereby the latter would challenge the enforceability or validity of the present Agreement.

6.2 Nothing in the Agreement shall be construed as:

- Creating a warranty as to the grant, validity or scope of any of any of the Patent Rights in a country of the Territory;

- Creating a warranty as to the non-violation, past, present or future of any third party patent or right,

- Creating a warranty as to the safety, the fitness for a particular purpose or the performance of the Patent Rights under the Agreement,

- Creating a warranty as to the non violation or absence of abusive use by a third party of the Patent Rights.

6.3 Hazards, risks and perils related to the performance of the Agreement and potential legal defects contained in one or more Patent Rights rest upon the sole Licensee who accepts them. Therefore, in case of non-grant, or cancellation of one or more of the Patent Rights, of dependence of the said Patent Rights upon a prior patent right, in the event that the Products, because of the use of the Patent Rights were declared as infringing or breaching third parties rights according to a definitive court ruling; the Co-Owners and/or Inserm Transfert will not be required to reimburse any sum already owed nor to decrease of the sums owed until the definitive court ruling, nor to pay potential damages to Licensee for the compensation of the damage caused by the said non-grant, cancellation, dependence, infringement or breach of third parties rights.

6.4 Licensee shall guarantee Inserm Transfert, the Co-Owners and their staff members, against any and all claims alleging personal injury or property damages arising from possession or use of the Patent Rights and the manufacture or marketing of Products by Licensee, its Affiliates or

its Sublicensees. Licensee renounces to bring any action against Inserm Transfert and/or the Co-owners in the case these complaints, requests, claims or actions are brought against Licensee or its Affiliates or its Sublicensee by third parties. Licensee shall not enter into any settlement agreement stating any fault on behalf of Inserm Transfert and/or the Co-Owners or which may otherwise adversely affect Inserm Transfert and/or the Co-Owners without obtaining their prior consent, which shall not be unreasonably withheld.

Licensee undertakes to request from its Affiliates and its Sublicensees the same commitment as that taken by Licensee in this present article; this obligation shall clearly appear in all sub-license agreements.

6.5 Licensee shall ensure that itself, its Affiliates and Sublicensees have an adequate liability insurance policy with a level of coverage consistent in order to cover their liability under the exercise of the present license (and especially under any clinical trial) and shall be able to prove it upon request of Inserm Transfert.

6.6 Licensee, its Affiliates and Sublicensees will be solely responsible for ensuring that the Products are in compliance with all applicable laws and regulations. Licensee, its Affiliates and Sublicensees will not call for the warranty from Inserm Transfert and/or the Co-Owners and will be solely responsible towards their customers and/or any third party for the quality and performance of the Products.

7.
CONFIDENTIALITY

7.1 Each Party undertakes to maintain confidential and not to pass on or disclose to anyone without a written authorization of the other Party, any information of any kind or of any form that the other Party may become aware of (in particular but not limited to all documents, and/or software data, and/or materials, samples, models, methods, descriptions, processes, applications, and or patentable or non-patentable knowledge) upon the performance the Agreement and notably any confidential information related to the Development Activities, the Patent Rights and the Products that it could receive in the framework of the performance of the Agreement, including without limitation any information exchanged in the negotiation of this Agreement (hereinafter "**Information**").

7.2 However, the following is not considered as confidential, Information as to which the receiving Party can prove:

- that it is disclosed or made available to the public further to a common agreement between the Parties, or it is disclosed by the Party to which it belongs ;
- that it was in the public domain at the time of the disclosure or it became publicly known other than through an act or mistake of the receiving Party ;
- that it was lawfully provided from a third party having the right to dispose of such information;
-that it was already in the possession of the receiving Party at the time of the disclosure

by the disclosing Party or was independently developed by its agents or employees without reliance on the Information received,

- that it was disclosed by virtue of mandatory law or regulation, or according to a definitive court ruling or arbitration award, so as to be in compliance with the regulations in force.

Nevertheless, in those last cases, the liability of the Party being compelled to disclose Information could be triggered if one of the following conditions has not been respected:

- it shall previously inform in writing the disclosing Party of the obligation to disclose, in such a way that said Party has enough time to oppose it or minimize its scope, as necessary;
- it shall limit the disclosure to what is strictly necessary in order to fulfill its obligations.

7.3 It is expressly agreed between the Parties that the disclosure by the Parties between them of Information under the Agreement, cannot be, in any case, interpreted as giving in an express or implied way to the receiving Party any right (according to a license or by any other mean) on such Information, other than the right expressly granted under the Agreement.

In any case, the burden of proof that Information is not confidential rests upon the Party which has received it.

7.4 Licensee shall have the right to provide Information to third parties, including its Affiliates and its Sublicensees, to the extent that the disclosure of such Information is useful or necessary to the Licensee for the exploitation of the license rights granted hereunder provided that the third Parties to which Information is disclosed are bound by an obligation of confidentiality similar to the one contained hereinabove.

7.5 The Parties undertake to take all reasonably required measures in order to comply with their obligations under the present Article 7 by their personnel and any person in the service of the Parties for any purpose whatsoever. Licensee shall include similar confidential obligations in the potential sublicense agreements that it may grant to Sublicensees.

7.6 Licensee undertakes, if requested by one or more Co-Owners, to affix on promotional material and/or on the packaging of the Products the mention “license [name of relevant Co-Owners]” or any other equivalent mention previously agreed to the Co-Owners. Any use by Licensee of the name of Inserm Transfert, Co-Owners or one of their employees, written or spoken, notably promotional, whatever the support used (video, poster, press release, press pack…) shall obtain the prior approval from the concerned person. This provision will remain in force notwithstanding the expiration or the termination of the present Agreement.

7.7 Inserm Transfert and the Co-Owners acknowledge that Licensee, its Affiliates or Sublicensees may have to disclose this Agreement and/or the existence thereof in accordance with SEC rules, or any other legislation governing publicly traded companies; where required, as advised by external legal counsel of the party concerned, such party shall have the right to file a redacted – or if the requirements specify that the Agreement shall not be redacted, a non-

redacted copy – of the Agreement to a public source indicated by such legislation.

7.8 The present obligation of confidentiality will remain in force for the duration of the Agreement and shall survive the expiration or termination of the Agreement, whatever the reason, for ten (10) years after the expiration or termination of the Agreement.

8
TERMINATION OF THE AGREEMENT

8.1 The present Agreement may be terminated ipso jure by one of the Parties (or in case of breach by Licensee, be converted into a non-exclusive license with respect to the Patents Rights at the discretion of Inserm Transfert) in case the other Party is in breach of any provision of this Agreement, and especially under Article 4, and the breach has not been remedied within sixty (60) days after receipt of written notice specifying the breach.

8.2 Licensee shall quickly inform Inserm Transfert in the event that Licensee is in situation of cessation of payments. In case Licensee becomes the subject of voluntary or involuntary winding-up proceedings or judicial recovery, Licensee shall quickly inform in writing Inserm Transfert. Inserm Transfert may terminate the Agreement ipso jure by written notification to Licensee, subject to the application of Articles L.622-13 and L.641-10 of the French Commercial Code. The termination of the Agreement will enter into force on the day Licensee receives the written notification.

8.3 The present Agreement may be terminated by Inserm Tranfert or may be converted into a non-exclusive license as regards to the Patent Rights and at the discretion of Inserm Transfert, in the cases provided for in Articles 3.5 and/or 3.6 of the Agreement.

8.4 In case of termination of the Agreement, Licensee undertakes not to exploit the Patent Rights or let them be exploited whether directly or indirectly until their expiration.

8.5 In the event of termination, Licensee, its Affiliates and Sublicensees shall have the right to sell any existing inventory of Products in the Territory for a maximum of six (6) months following any such termination; provided, however, that Licensee (i) shall provide Inserm Transfert with a Products inventory statement at the termination date and (ii) shall have fully complied and will fully comply, for the further disposal of Products, with the financial provisions of Article 4 hereof.

8.6 Moreover, in case of termination or expiration of the Agreement and under Inserm Transfert instructions, Licensee undertakes to return or destroy all Information, materials and documents received from Inserm Transfert, it being understood that Licensee may nevertheless keep a copy of the Information in secured files for archiving purposes only.

8.7 In the event that this Agreement is terminated and a Sublicense Agreement has been granted under this Agreement, Inserm Transfert and Co-Owners shall respect the rights obtained by any such Sublicensee, and this Agreement may become an agreement between Inserm

Transfert and Co-Owners and any such Sublicensees subject to the Sublicensee(s) agreeing to be bound under this entire Agreement, and provided that that the sublicensee agreement has been signed in accordance with the provision of Articles 1.2 of the Agreement.

8.8 More generally, the provisions of Articles 6, 7, 8.5, 9 and 10 shall survive the expiration or the termination of the Agreement.

9
MISCELLANEOUS

9.1 Inalienability

The Agreement is concluded intuitu personae and shall not be assigned or transferred or continue for any reason without Inserm Transfert's prior written and express approval, including any transfer or continuation according to a legal provision or an imperative regulation, a recovery or a winding-up by Court, or under any other decision or injunction, purchase, merger, transfer, division, lease or any other disposition of all or practically all assets or activities of Licensee to which the Agreement relates.

The Agreement shall continue in case of direct or indirect change of Control by Licensee - "Control" shall mean the ownership of more than fifty percent (50%) of the voting rights or of the rights to direct the management and policies of an entity.- or of total transmission of the assets and liabilities of Licensee, except if (i) such continuance conflicts with the public order/ethical obligations of Inserm Transfert and/or the Co-Owners and/or (ii) this action tarnishes the image of Inserm Transfert and/or the Co-Owners and/or (iii) the Co-Owners and/or Inserm Transfert are currently involved or have been involved in a litigation with beneficiary within the three (3) years prior to the notification from Licensee and can provide written evidence of such litigation. Inserm Transfert may terminate the license for one of the reasons described above within twenty-one (21) days following the notification by Licensee announcing the planned change of Control or the total transmission of assets and liabilities. In the absence of reply or objection of Inserm Transfert in the said period, the Agreement shall continue.

Notwithstanding the above, the Agreement may be freely assigned or transferred to Affiliates, or the rights and obligations of Licensee may be freely delegated to Affiliates, upon prior information of Inserm Transfert and provided that such assignment / transfer / delegation (i) does not conflict the public order / ethical obligations of Inserm Transfert and/or the Co-Owners and/or (ii) does not tarnish the image of Inserm Transfert and/or the Co-Owners and/or that (iii) the Co-Owners and/or Inserm Transfert are not currently involved or have not been involved in a litigation with the Affiliate within the three (3) years prior to the notification from Licensee. In case of delegation to its Affiliates, Licensee shall remain responsible towards the other Parties for the performance by its Affiliates of all the obligations binding upon Licensee under the present Agreement.

It is hereby agreed that any company to which the rights and obligations of Licensee have been assigned, transferred or delegated shall be subject to the same obligations as that binding upon Licensee under the present Agreement, unless that the new parties agree otherwise.

Any change of the terms and conditions of the present Agreement which would be agreed and would occur consequently to the said transfer/assignment, for instance the name and the address of the assignee, shall be stipulated in writing and be inserted as an amendment to the present Agreement at the time of the said assignment or transfer.

9.2. Independent Contractors

The present Agreement shall not in any case be interpreted as creating an association or a de facto partnership between the Parties, each of them to be considered as an independent co-contracting party.

9.3 Entirety of the Agreement

The Agreement puts to an end and replaces any previous agreement, written or spoken, between the Parties on the same subject matter and constitutes the entire agreement between the Parties relating to its subject matter.

Any addition or modification of the terms of the Agreement shall be acknowledged by an amendment to the Agreement.

9.4 Communications

Any communication or notification to the attention of the Parties shall be done by registered letter with acknowledgment of receipt to the address indicated below, for as long as the Parties have not been notified by a change of address in writing.

To Inserm Transfert:
Inserm Transfert SA
7 rue Watt
75013 PARIS

To Licensee :
ProQR Therapeutics IV B.V.
Attn. Sarah Hafith, VP Innovation BD
Zernikedreef 9
2333 CK Leiden
The Netherlands

With copy to the Legal Department
Zernikedreef 9
2333 CK Leiden
The Netherlands
****

Day to day communications may be done by any written means.

9.5 Declaration or public communication

Any declaration or public communication regarding the signature of the present Agreement or its content shall only be done only with the consent of all Parties.

9.6 Waiver of rights

In case of a breach by one or the other Party of any of its obligations under the Agreement, if a Party fails to enforce its rights, the non exercise of its rights shall not be interpreted as a waiver to exercise its rights in the future or in case of a new similar breach of any obligation by the breaching Party resulting from the present Agreement.

9.7 Registration

Licensee shall assume, at its own costs and receive all powers to carry out any registration formalities of the present Agreement, in particular any tax registration and registration on the relevant national patent registries in the countries of the Territory subject of the present license.

9.8 Force Majeure

Each Party shall be excused not to fulfill its obligation and shall neither be responsible nor accountable for damages towards the other Party(ies), if the non performance is due to a force majeure event, such as the disruption of services in particular resulting from strikes, resignation or any event outside of its control. The Party which cannot perform its contractual obligations as a result of a force majeure event shall immediately notify the other Party(ies) in writing. Should such breach or the late in the performance resulting from a force majeure event last for more than three (3) months after notification, the other Party(ies) may terminate the Agreement at any time upon notification to the other Party.

9.9 Severability

If one or several provisions of the Agreement shall be found invalid or declared as such under a treaty, a law, or a regulation or by a final decision of a court having jurisdiction, the other provisions shall keep all their force and scope. The Parties shall immediately make the necessary changes by respecting, as far as possible, the agreement existing at the time of signature of the Agreement.

10.
GOVERNING LAW AND DISPUTE RESOLUTION

The agreement shall be governed by French Law.

Any dispute or controversy relating to the Agreement that cannot otherwise be settled by them within three (3) months following the notification by the more diligent Party will be settled by a French court of competent jurisdiction located in Paris.

Drawn up in Paris and Leiden,

CONFIDENTIAL

In three (3) originals

Inserm Transfert **Licensee**

Chairman of the Management Board
Pascale AUGE

AP-HP

Florence FAVREL-FEUILLADE
Director of the Clinical Research and Innovation Department

Appendix 1

DEVELOPMENT PLAN

- Initiation of a clinical trial more advanced than the First in Man for a first Product, such as a phase IIb or pivotal phase : ****

- Initiation of Phase phase III for a first Product: ****– if required for NDA submission

- NDA or equivalent submission for a first Product: ****if phase III required (****if phase III not required)

- NDA or equivalent obtaining for a first Product: ****if phase III required (****if phase III not required)

- First commercialization of a first Product: ****if phase III required (****if phase III not required)

Exhibit 4.16

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.

February 9, 2018

Development Program: QRX 421 (USH2A-exon 13)

Amount of Award: Up to $7.5 million

Name of Awardee: ProQR Therapeutics IV B.V. ("ProQR")

Dear Daniel de Boer:

We are pleased to inform you that the Foundation For Fighting Blindness Clinical Research Institute ("FFB") is hereby issuing the Award, up to the amount indicated above, for the Development Program described in Exhibit A and disbursed in accordance with Exhibit B. The awardee, ProQR, shall be responsible for the remaining funds to establish proof of concept in patients for the Product (estimated to be an additional $7.5 million) and for all remaining costs required to complete the Development Program and for costs associated with continuing Commercially Reasonable Efforts necessary to further develop and commercialize the Product. Each party's obligations hereunder will commence and apply upon the execution of this Agreement. The Award is subject to the following terms, conditions and policies of this Letter Agreement ("Agreement"):

1. Disbursement of Award; FFB Know-How; Reports.

(a) The Award will be disbursed by FFB to ProQR in accordance with the Milestone Payment Schedule set forth in Exhibit B. Any FFB funds not expended on the Development Program must be returned to FFB, and upon such return, the amounts of such returned funds will not be included as part of the Actual Award for purposes of calculating any royalties or other amounts owed by ProQR to FFB pursuant to Paragraph 2.

(b) To the extent FFB provides or makes available any information, expertise, know-how or other intellectual property related to Usher Syndrome or the treatment, prevention, or cure thereof ("FFB Know-How") to ProQR, FFB hereby grants to ProQR a non-exclusive, transferable, sublicensable (through multiple tiers), worldwide right and license under all of FFB's rights in such FFB Know-How to assist ProQR to

research, develop, commercialize, make, have made, use, sell, have sold, offer for sale, import, export and otherwise exploit the Product.

(c) ProQR agrees to provide FFB and the Joint Development Committee ("JDC") specified below with a reasonably detailed, written report every three (3) months, summarizing progress toward achieving the goals of the Development Program. In addition, ProQR shall prepare and deliver to FFB a closing report within thirty (30) days after the completion of the Development Program.

2. Royalties. In consideration of FFB's Award under this Agreement, ProQR agrees to pay to FFB royalties as follows:

(a) ProQR shall pay ****FFB **** as follows:

(i) **** upon ****;

(ii) **** upon **** ;

(iii) ****upon ****

(iv) **** upon **** Such amounts shall be paid by ProQR no later than the first within sixty (60) days following each of the dates specified.

(b) In the event of a license, sale or other transfer of the Product or the rights to the ProQR Development Program Technology to develop and commercialize the Product (excluding Net Sales), or in the event of a Change of Control Transaction (collectively a "Disposition Transaction"): (i) ProQR shall pay to FFB ****, ****(the "Disposition Payment"), and the amounts specified in Sections 2(a)(i)-(iv) shall each be reduced by one fourth of the Disposition Payment; and (ii) FFB may elect, by providing notice to ProQR within forty five (45) days of a Disposition Transaction, not to pay any remaining portion of the Award, provided that, in the event such election is not made, FFB shall make the remaining portion of the Award in accordance with this Agreement, and, without regard to any such election, ProQR and its licensees, transferees, and successors shall remain liable for the royalties specified in Section 2(a) of this Agreement. The Disposition Payment shall be made within sixty (60) days after any Disposition Transaction.

(c) In case of any delay in any payment by ProQR to FFB pursuant to this Section 2, Interest shall be calculated from the tenth (10^{th}) day after the date upon which the applicable payment first becomes due from ProQR.

(d) In the event of a Disposition Transaction, ProQR shall cause the licensee, buyer or other transferee to agree in a writing in which FFB is specified as a third party beneficiary to be jointly and severally liable with ProQR for the royalties specified in Sections 2(a) and 2(b).

3. Commercially Reasonable Efforts. ProQR shall use Commercially Reasonable Efforts to conduct the Development Program during the term of this Agreement. After the Development Program is completed, ProQR shall exercise Commercially Reasonable Efforts to develop the Product and shall continue to report to FFB annually on the progress of its development activities regarding the Product until the earlier of the First Commercial Sale of the Product or such research efforts are abandoned by ProQR, its Affiliates and its sublicensees, solely as a result of scientific failure.

4. Joint Development Committee ("JDC").

(a) ProQR shall have the day to day control of the decisions regarding the Development Program. However, ProQR and FFB shall form a JDC to: (i) oversee the Development Program; (ii) determine whether payment milestones have been achieved; (iii) determine if any proposal constitutes a Disposition Transaction and in case such Disposition Transaction does not constitute a Change of Control Transaction, to approve such Disposition Transaction but solely with respect to verifying if the agreement for such license, sale or other transfer preserves FFBs rights under this Agreement ; (iv) consider any proposal to change or revise the Budget (as attached in Exhibit A) or the amount or timing of the milestone payments; and (v) consider other issues related to the Development Program raised by either party, provided that, the JDC must unanimously approve any matter set forth in (ii), (iii) and (iv) above in order to proceed with such matter.

(b) The JDC shall consist of two (2) individuals appointed by ProQR and two (2) individuals appointed by FFB. One of such individuals from ProQR and FFB, respectively, shall be the principal liaison to the Development Program. The principal liaison chosen by ProQR shall serve as the chairperson of the JDC and shall prepare and circulate minutes of each meeting no later than ten (10) days following each meeting. Either party may replace the individuals appointed by such party and designate a different individual as the principal liaison upon written notice to the other party.

(c) The JDC shall meet no less than quarterly, and more often at the request of the principal liaison of either party. Such meeting may be held face to face or by telecommunication methods with which each member of the JDC can hear and respond to the other members.

(d) The JDC shall terminate and cease to exist on the earlier of the First Commercial Sale or the termination of this Agreement.

5. Interruption License. Upon written notice from FFB following an Interruption (the "Interruption Notice"), ProQR shall elect, within thirty (30) days of such Interruption Notice, one of the following options by notice to FFB:

(a) ProQR shall reasonably demonstrate, in the form of a written progress report, that an Interruption has not occurred, or that ProQR, an Affiliate thereof, or a licensee or sublicensee or other transferee of either of the foregoing is exercising Commercially Reasonable Efforts to research, develop or commercialize the Product;

(b) ProQR shall provide FFB with notice within such thirty (30) day period that ProQR, an Affiliate thereof, or a licensee or sublicensee or other transferee of either of the foregoing, has plans to resume Commercially Reasonable Efforts to develop or commercialize the Product and resumes such Commercially Reasonable Efforts within the ninety (90) day period following such notice; provided that the notice included in this subparagraph (b) shall be effective only once; or

(c) ProQR shall grant FFB an Interruption License, as set forth below.

If ProQR has elected (a) or (b) above within thirty (30) days of the Interruption Notice, the Interruption Notice shall be deemed satisfied and be of no further force or effect unless FFB notifies ProQR within thirty (30) days after receipt of ProQR's progress report under (a) above or provides notice under (b) above that FFB disputes such progress report or notice, as the case may be. If FFB provides timely notice of its dispute, the parties shall resolve such dispute in accordance with the dispute resolution provision in Section 11(b) of this Agreement.

If ProQR has elected (a) or (b) above and FFB has disputed such election, the resolution of the dispute is concluded, and the final outcome of such dispute resolution is that such election was defective, ProQR shall be deemed to have made the election specified in (c) above.

If ProQR has made (or is deemed to have made) the election specified in (c) above, ProQR hereby grants to FFB an Interruption License effective upon such election (or deemed election) (such date, the "Interruption License Effective Date"). The Interruption License shall be an exclusive (even as to ProQR), worldwide license to FFB under the Product and the ProQR Development Program Technology and to use the same to manufacture, have manufactured, license, use, sell, offer to sell, and support the Product in the Field. ProQR shall deliver to FFB, within ninety (90) days after the Interruption License Effective Date, a copy of all materials and data in its possession or control generated in the performance of the Development Program and ProQR Development Program Technology, to the extent required by FFB to make, use, or sell the Product in the Field. In the event that ProQR assigns all of or certain of its rights and obligations to develop and commercialize the Product at any time to a third party, such third party shall be subject to the obligations of the Interruption License. The Interruption License shall be deemed to constitute intellectual property as defined in Section 365(n) of the U.S. Bankruptcy Code. ProQR agrees that FFB, as a licensee of such rights, shall retain and may exercise all of its rights and elections under the U.S. Bankruptcy Code; provided, however, that nothing in this Agreement shall be deemed to constitute a present exercise of such rights and elections.

6. Indemnification by ProQR and FFB.

(a) ProQR shall indemnify, defend and hold harmless FFB, its Affiliates, and their respective directors, officers, employees, consultants, committee members, volunteers, agents and representatives and their respective successors, heirs and assigns (each, an "FFB Indemnitee"), from and against any and all claims, suits and demands of third parties and losses, liabilities, damages for personal injury, property damage or

otherwise, costs, penalties, fines and expenses (including court costs and the reasonable fees of attorneys and other professionals) payable to such third parties arising out of, and relating to any such third party claims resulting from:

(i) the conduct of the Development Program by ProQR or its Affiliates or their respective directors, officers, employees, consultants, agents, representatives, licensees, sublicensees, subcontractors and/or investigators (each, a "ProQR Party") under this Agreement and/or pursuant to one or more agreements between ProQR and any ProQR Party, or any actual or alleged violation of law resulting therefrom;

(ii) ProQR's or its Affiliates' development, manufacture, or commercialization of the Product; and

(iii) any claim of infringement or misappropriation with respect to the conduct of the Development Program by or on behalf of ProQR and its Affiliates', or ProQR's or its Affiliates' licensees sublicensees or transferees manufacture, use, sale, or import of the Product.

(b) FFB will indemnify, defend and hold harmless ProQR, its Affiliates and their respective directors, officers, employees, consultants, agents and representatives and their respective successors, heirs and assigns ("ProQR Indemnitees") from and against any and all claims, suits and demands of third parties and losses, liabilities, damages for personal injury, property damage or otherwise, costs, penalties, fines and expenses (including court costs and the reasonable fees of attorneys and other professionals) payable to such third parties arising out of, resulting from, or relating to any exercise of any rights under the Interruption License by or on behalf of FFB, any designee, assignee or successor in interest thereto, or any licensee or sublicensee of any of the foregoing, except to the extent the claim, suit, demand, liability, damage or loss results from the negligence or willful misconduct of a ProQR Indemnitee after the effective date of the Interruption License.

(c) A party entitled to indemnification under this Paragraph 6 (the "Indemnified Party") will promptly notify the other Party (the "Indemnifying Party") of any claims, suits, demands, losses, liabilities, damages costs, penalties, fines, or expenses subject to indemnification under this Paragraph 6 of which it is made aware. The Indemnified Party will cooperate, and exert efforts to cause other Indemnified Parties to cooperate, in assisting the Indemnifying Party in presenting a defense, if requested to do so. The Indemnifying Party shall have sole control to select defense counsel, direct the defense of any such complaint or claim, and the right to settle claims at the Indemnifying Party's sole expense, provided that any such settlement does not incur non-indemnified liability for or admit fault by any Indemnified Party. In the event a claim or action is or may be asserted, the Indemnified Party shall have the right to select and to obtain representation by separate legal counsel. If the Indemnified Party exercises such right, all costs and expenses incurred for such separate counsel shall be borne by the Indemnified Party. No Indemnified Party shall settle or enter into any voluntary disposition of any matter subject to indemnification under this Paragraph 6 without the prior written consent of the Indemnifying Party, such consent not to be unreasonably withheld.

7. Insurance. ProQR shall maintain at its own expense, with a reputable insurance carrier, coverage for ProQR, its Affiliates, and their respective employees written on a per occurrence basis commensurate with a reasonable assessment of the risks associated with the development efforts being conducted by ProQR, the following policies: Commercial general liability insurance, including contractual liability as respects this Agreement for bodily injury and property damage and, no later than the first use administration of the Product to a human subject, the Product liability and clinical trials liability.

Maintenance of such insurance coverage will not relieve ProQR of any responsibility under this Agreement for damage in excess of insurance limits or otherwise. On or prior to the effective date of this Agreement, ProQR shall provide FFB with an insurance certificate from the insurer(s), broker(s) or agent(s) (hereinafter collectively the "Insurance Providers") evidencing the applicable insurance coverage. At its request, FFB may review ProQR's insurance coverage with relevant ProQR personnel no more than one time per year.

8. Intellectual Property Rights. All inventions, data, know-how, information, results, analyses, and other intellectual property rights resulting from the Development Program shall, as between the parties, be owned by ProQR and the preparation, filing and maintenance of all patents resulting from the Development Program shall, as between the parties, be the sole responsibility, and under the sole control, of ProQR. Subject to Paragraph 5, FFB hereby assigns and transfers to ProQR all of FFB's right, title, and interest in and to all inventions and other intellectual property resulting from the Development Program, FFB's access to, or knowledge or use of, any ProQR Development Program Technology, the Product, or confidential or proprietary information of ProQR, and all intellectual property rights related to any of the foregoing, free and clear of all liens, claims, and encumbrances.

9. Termination of Agreement.

(a) Either party may terminate this Agreement for cause, without prejudice to any other remedies available to the terminated party with respect thereto, by providing the other party with written notice of such cause and intent to terminate; provided, however, that the other party shall have thirty (30) days following the receipt of written notice to cure such cause. For this Paragraph 9, "cause" shall mean (i) a party's material breach of its covenants or obligations under this Agreement, (ii) a bankruptcy or similar filing by a party or a proceeding under the applicable bankruptcy laws or under any dissolution or liquidation law or statute now or hereafter in effect and filed against such party or all or substantially all of its assets if such filing is not dismissed within sixty (60) days after the date of its filing, or (iii) ProQR's material failure to achieve any Milestone within ninety (90) days of its anticipated achievement day.

(b) The following provisions shall survive the termination of this Agreement in case of termination by FFB: Paragraphs 2, 3, 5 6, 8, 9, 10, 11, and 12.

10. Audits. At the request of FFB, from time to time, ProQR shall permit FFB, upon reasonable notice, to audit and examine such books and records of ProQR as may be necessary for verifying ProQR's expenditures of the Award and the payment of royalties, if any, but no more frequently than once every calendar year. All non-public information made available by ProQR as part of any such audit, as part of any other reports (whether written or non-written), or otherwise under this Agreement (including, but not limited to, in connection with the JDC) shall be regarded as ProQR's confidential information and FFB hereby covenants that, except to the extent required by law (provided that FFB promptly notifies ProQR of such requirement and permits ProQR to seek, and reasonably cooperates with ProQR at ProQR's expense in seeking, a protective order therefor or other confidential treatment thereof), it shall not use any such information for any purpose other than determining whether ProQR has complied with its obligations hereunder, and shall maintain such information in confidence in a manner at least as restrictive as its manner of treating its own confidential information of similar nature and in any event not less than with a reasonable degree of care.

11. Miscellaneous.

(a) Governing Law. This Agreement shall be governed by and construed in accordance with the internal laws of the State of Maryland.

(b) Dispute Resolution.

(i) In the event of any dispute, claim or controversy arising out of, relating to or in any way connected to the interpretation of any provision of this Agreement, the performance of either party under this Agreement or any other matter under this Agreement, including any action in tort, contract or otherwise, at equity or law (a "Dispute"), either party may at any time provide the other party written notice specifying the terms of such Dispute in reasonable detail. As soon as practicable after receipt of such notice, an officer of each party shall meet at a mutually agreed upon time and location to engage in good faith discussions for the purpose of resolving such Dispute. If the Dispute is not resolved within thirty (30) days of such notice, either party may institute arbitration in accordance with (ii) below.

(ii) In the event any Dispute is not resolved in accordance with (i) above, such Dispute shall be resolved by final and binding arbitration. Whenever a party decides to institute arbitration proceedings, it shall give written notice to that effect to the other party. Arbitration shall be held in Washington, D.C., according to the then-current commercial arbitration rules of the Center for Public Resources ("CPR"), except to the extent such rules are inconsistent with this subparagraph. The arbitration will be conducted by one (1) independent, neutral arbitrator who shall be mutually acceptable to both parties, such acceptance not to be unreasonably withheld, and who shall be appointed in accordance with CPR rules. If the parties are unable to mutually agree on such an arbitrator, then the arbitrator shall be appointed in accordance with CPR rules. Any arbitrator chosen hereunder shall have educational training and industry experience sufficient to demonstrate a reasonable level of relevant scientific, financial, medical and industry knowledge. The arbitrator shall not

have the power to award punitive damages. The proceedings and decisions of the arbitrator shall be confidential, final and binding on all of the parties. Judgment on the award so rendered may be entered in any court having jurisdiction thereof. The parties shall share the costs of arbitration according to the decision of the arbitrator. Nothing in this subparagraph will preclude either party from seeking equitable or injunctive relief, or interim or provisional relief, from a court of competent jurisdiction, including a temporary restraining order, preliminary injunction, or any other form of permanent or interim equitable or injunctive relief, concerning a dispute either prior to or during any arbitration.

(c) This Agreement may be executed in two (2) or more counterparts, each of which shall be deemed to be an original, but all of which together shall constitute one and the same Agreement. Facsimile and other electronically scanned signatures shall have the same effect as their originals.

(d) All communications between the parties with respect to any of the provisions of this Agreement will be sent to the addresses set out below, or to such other addresses as may be designated by one party to the other by notice pursuant hereto, by prepaid, certified air mail (which shall be deemed received by the other party on the seventh (7^{th}) business day following deposit in the mail), or by facsimile transmission or other electronic means of communication (each of which shall be deemed received when transmitted), with confirmation by first class letter, postage pre-paid, given by the close of business on or before the next following business day:

if to FFB, to:

Ben Yerxa, Ph.D.
Chief Executive Officer
7168 Columbia Gateway Drive
Suite 100
Columbia , Maryland 21046
****

with a copy to:

Schaner & Lubitz, PLLC
4550 Montgomery Ave., Suite 1100 N
Bethesda, Maryland 20814
Attn: Kenneth I. Schaner, Esq.
****

if to ProQR, to:

Daniel de Boer, CEO
Zernikedreef 9
2333 CK, Leiden
the Netherlands
****

With a copy to: ****

(e) The paragraph headings are for convenience only and will not be deemed to affect in any way the language of the provisions to which they refer.

(f) ProQR will not, by amendment of its organizational or governing documents, or through reorganization, recapitalization, consolidation, merger, dissolution, sale, transfer or assignment of assets, issuance of securities, or any other voluntary action, avoid or seek to avoid the observance or performance of any of the terms, provisions, covenants or agreements of this Agreement.

(g) This Agreement may not be assigned by any party without the consent of the other party, except that either Party may assign this Agreement without such consent to an Affiliate of such party or in connection with the transfer, whether by sale of assets, merger or otherwise, of all or substantially all of the assets or business of such party to which this Agreement relates. Any assignment that is not in accordance with this subparagraph 11(g) will be null and void *ab initio*.

(h) Nothing herein contained shall be deemed to create an agency, joint venture, amalgamation, partnership or similar relationship between FFB and ProQR. Notwithstanding any of the provisions of this Agreement, neither party to this Agreement shall at any time enter into, incur, or hold itself out to third parties as having authority to enter into or incur, on behalf of the other party, any commitment, expense, or liability whatsoever, and all contracts, expenses and liabilities in connection with or relating to the obligations of each party under this Agreement shall be made, paid, and undertaken exclusively by such party on its own behalf and not as an agent or representative of the other.

(i) FFB and ProQR shall agree on any press release or other public announcement, other than an academic, scholarly, or scientific publication, concerning the terms of this Agreement or this Award prior to its public release, except to the extent any such release or announcement is required by law, rule, or regulation or the rules of any securities exchange. The parties agree that they intend to advance the body of general scientific knowledge of Ushers Syndrome and its potential therapies and cures and the parties acknowledge that ProQR shall, as commercially and scientifically reasonable based on the results of the Development

Program, publish the results of the Development Program in a scientific peer-reviewed publication on a timely basis. FFB's support for the Development Program shall be acknowledged in any press releases and publications relating to the Development Program.

(j) In accordance with the U.S. Department of the Treasury Anti-Terrorist Financing Guidelines, ProQR shall take reasonable steps to ensure that the payments received from FFB are not distributed to terrorists or their support networks or used for activities that support terrorism or terrorist organizations. ProQR certifies that it is in compliance with all laws, statutes and regulations restricting U.S. persons from dealing with any individuals, entities, or groups subject to Office of Foreign Assets Control (OFAC) sanctions.

12. Definitions.

Unless otherwise defined in this letter, the following shall apply:

· "Award" shall be the maximum amount to be paid by FFB to ProQR as specified in this Agreement.

· "Actual Award" means the total amount of the Award actually paid to ProQR by FFB.

· "Affiliate" shall mean, with respect to a party, any entity, which directly or indirectly controls, is controlled by, or is under common control with, such party. For these purposes, "control" shall refer to (a) the ownership, directly or indirectly, of at least fifty percent (50%) of the voting securities or other ownership interest of an entity; or (b) the possession, directly or indirectly, of the power to direct the management or policies of an entity, whether through the ownership of voting securities, by contract or otherwise.

· "Approval" shall mean all approvals from the relevant regulatory authority in a given country necessary to market and sell a pharmaceutical product in such country, including pricing and reimbursement approvals if required for marketing or sale of such product in such country.

· "Change of Control Transaction" shall mean the consummation of a transaction, whether in a single transaction or in a series of related and substantially contemporaneous transactions, constituting (i) a merger, share exchange or other reorganization, (ii) the sale by one or more stockholders of a majority of the voting power of ProQR, or (iii) a sale of all or substantially all of the assets of ProQR (or that portion of its assets related to the subject matter of this Agreement), in which the stockholders of ProQR immediately prior to such transaction do not own a majority of the voting power of the acquiring, surviving or successor entity, as the case may be; provided that a Change of Control Transaction shall not include a bona fide financing transaction for the benefit of ProQR (i.e., in which ProQR raises capital for general working or business purposes) in which voting control of ProQR transfers to one or more persons or entities who acquire shares of ProQR, and the existing ProQR shareholders receive no consideration directly or indirectly in connection with the transaction.

· "Commercially Reasonable Efforts" or "CRE" shall mean the level of effort, expertise and resources that is substantially and materially consistent with industry standards for companies of similar size and

financial resources to research, develop and commercialize the Product, provided such research, development and commercialization is technically feasible, devoting the degree of attention and diligence to such efforts that is substantially and materially consistent with industry standards for a product at a comparable stage in development, with similar market potential, and taking into account, without limitation, issues of safety and efficacy, proprietary position, the regulatory environment, and other relevant scientific, technical and commercial factors, and for companies of similar size and financial resources.

· "Disposition Payment" shall have the meaning set forth in Section 2(b).

· "Disposition Transaction" shall have the meaning set forth in Section 2(b).

· "Field" shall mean the treatment of inherited retinal diseases.

· "First Commercial Sale" shall mean the first Sale of a Product in the Field by ProQR or an Affiliate, licensee, sublicensee, transferee or successor of ProQR in a country in the Territory following Approval of the Product in that country, or, if no such Approval or similar marketing approval is required, the date upon which a Product is first commercially sold in that country in an arms-length transaction. For clarity, the supply of a Product as part of a compassionate use or sampling program shall not constitute a First Commercial Sale.

· "Interest" shall mean the prime rate applicable during the relevant time period, as published in the *Wall Street Journal*, plus five (5) percentage points.

· "Interruption" shall mean the cessation of Commercially Reasonable Efforts to develop a Product for more than one hundred eighty (180) consecutive days at any time before the First Commercial Sale of the Product. For clarity, delays resulting from events outside of ProQR's reasonable control (e.g., technical difficulties, shortages of supplies or materials, delays in preclinical or clinical studies or regulatory processes, etc.) will not be deemed cessation of Commercially Reasonable Efforts.

· "Net Sales" shall mean, for any period, the gross amount received for sales of the Product in the Field by ProQR or any ProQR Affiliate, sublicensee or transferee as applicable (a "Selling Person"), to a non-Affiliate of the Selling Person, less the following deductions, in each case to the extent specifically related to the Product and taken by the Selling Person or otherwise paid for or accrued by the Selling Person ("Permitted Deductions"):

trade, cash, promotional and quantity discounts and inventory management fees paid to wholesalers;

tariffs, duties, excises and taxes on sales (including sales or use taxes or value added taxes) to the extent imposed upon and paid directly with respect to such sales (and excluding national, sales or local taxes based on income);

freight, insurance, packing costs and other transportation charges allocated to the sale;

invoiced amounts that are written off as uncollectible in accordance with Selling Person's accounting policies, consistently applied;

amounts repaid or credits taken by reason of damaged goods, rejections, defects, expired dating, recalls or returns or because of retroactive price reductions, billing errors, or trial prescriptions;

charge back payments, rebates and discounts granted to (i) managed healthcare organizations, (ii) federal, state or provincial or local governments or other agencies, (iii) purchasers and reimbursers, or (iv) trade customers, including wholesalers and chain and pharmacy buying groups;

discounts paid under state legislated or seller-sponsored discount prescription drug programs or reductions for coupon and voucher programs; and

documented custom duties actually paid by the Selling Person.

Sales of the Product between or among ProQR and its Affiliates and sublicensees for resale, or for use in the production or manufacture of the Product, shall not be included within Net Sales; provided, however, that any subsequent sale of the Product (or any Product produced or manufactured using the Product) by ProQR or its Affiliate or sublicensee or transferee to another non-Affiliate third party shall be included within Net Sales. Net Sales shall exclude any sale or other distribution for use in a clinical trial or other Development Program activity, for compassionate or named-patient use or for test marketing.

· "Product" shall mean QR-421a (USH2A-exon 13) and its derivatives and any commercial product containing the foregoing.

· "ProQR Development Program Technology" shall mean all Technology discovered or developed, or controlled, by ProQR or its Affiliates, as a result of the Development Program under this Agreement (solely for purposes of the Interruption License), including, without limitation, Technology owned or controlled by ProQR prior to ProQR's performance of the Development Program under this Agreement that is necessary in the performance of the Development Program under this Agreement. Without limitation, ProQR Development Program Technology shall include data, technical information, source codes, know-how, inventions (whether or not patented), trade secrets, laboratory notebooks, and processes and methods.

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· "Technology" shall mean any intellectual property rights and related know-how, data, technical information, source codes, inventions (whether or not patented), trade secrets, laboratory notebooks, and processes and methods.

· "Territory" shall mean worldwide.

We are pleased to make the Award described in this Agreement. Please indicate your agreement to the terms set forth in this Agreement by signing below.

Sincerely,

Foundation For Fighting Blindness Clinical Research Institute

By: _____

Name: _____

Title: _____

Agreed:

ProQR Therapeutics IV B.V.

By: _____

Name: _____

Title: _____

Exhibit A

Development Program Plan and Budget

The development milestones and costs for QRX-421a for USH2A-ex13 are summarized below, the total costs from the current status, clinical candidate selected, until NDA filing is ****.

Milestone	**Start of milestone***	**Total Cost (US dollars)**
1. Clinical candidate selected (completed)	****	****
o 2.Initiation of Tox studies	****	****
o 3. Initiation of GMP manufacturing and IND submission	****	****
o 4. Initiation of IND-enabling studies and phase 1b/ II clinical study	****	****
o 5. Initiation of maintenance study	****	****
o 6. Initiation of phase III clinical study	****	****
o 7. Filing of an NDA	****	****

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Exhibit B

Milestone Payment Schedule

Milestone	Payment Upon Initiation	Payment Upon Completion
Clinical Candidate Selection	****	****
Toxicity Studies in two species	****	****
GMP Manufacturing of sufficient Clinical supply and IND/CTA filing	****	****
Pre-IND Studies and 1b/2 clinical study	****	****
Maintenance Study*	****	****

*The Maintenance Study will not be undertaken unless the Phase 1b/2 Study demonstrates positive patient benefit/risk

Payments shall be made by FFB within forty-five (45) days of receipt from ProQR of the corresponding invoice and supporting documentation verifying occurrence of such milestone, the actual total cost to achieve the milestone incurred and JDC verification.

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, 2017.

- 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);
- Amylon Therapeutics 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 30, 2018

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 30, 2018

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, 2017, 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 30, 2018

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 consent to the incorporation by reference in the Registration Statement No. 333-199451 on Form S-8 and No. 333-207245 on Form F-3 of our report dated March 30, 2018 relating to the consolidated financial statements of ProQR Therapeutics N.V. appearing in this Annual Report on Form 20-F of ProQR Therapeutics N.V. for the year ended December 31, 2017.

/s/Deloitte Accountants B.V.

Amsterdam, the Netherlands
March 30, 2018