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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2020

OR

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

For the transition period from to

Commission file number: 001-36294

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

The Netherlands
(Jurisdiction of incorporation or organization)

Paasheuvelweg 25a,
1105 BP Amsterdam, The Netherlands
(Address of principal executive offices) (Zip Code)

+31-20-240-6000
(Registrant's telephone number, including area code)

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

Title of Each Class	Trading Symbol(s)	Name of Each Exchange on Which Registered
Ordinary shares, par value €0.05 per share	QURE	The Nasdaq Stock Market LLC (The Nasdaq Global Select Market)

Securities registered under Section 12(g) of the Act: **None**

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

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 every Interactive Data File required to be submitted 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 such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, 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. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act.) Yes ☐ No ☒

The aggregate market value of the voting and non-voting ordinary shares held by non-affiliates of the registrant as of June 30, 2020 was $2,002.7 million, based on the closing price reported as of June 30, 2020 on the NASDAQ Global Select Market.

As of February 25, 2021, the registrant had 44,993,987 ordinary shares, par value €0.05, outstanding.

The documents incorporated by reference are as follows:

Portions of the registrant's definitive Proxy Statement for its 2021 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than April 30, 2021 and to be delivered to shareholders in connection with the 2021 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Annual Report on Form 10-K.

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SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" as defined under federal securities laws. Forward-looking statements are based on our current expectations of future events and many of these statements can be identified using terminology such as "believes," "expects," "anticipates," "plans," "may," "will," "projects," "continues," "estimates," "potential," "opportunity" and similar expressions. These forward-looking statements, which include, but are not limited to, statements related to the COVID-19 coronavirus pandemic, our collaboration and license agreement with CSL Behring LLC and the timing of the completion of the transactions contemplated thereby, our beliefs about our competitive advantage and the capabilities of our manufacturing facility, our cash runway, the advancement of our clinical trials, our intellectual property portfolio, and the impact of regulatory actions on our regulatory submission timelines, may be found in Part I, Item 1 "Business," Part 1, Item 1A "Risk Factors," Part II, Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" and other sections of this Annual Report on Form 10-K.

Forward-looking statements are only predictions based on management's current views and assumptions and involve risks and uncertainties, and actual results could differ materially from those projected or implied. The most significant factors known to us that could materially adversely affect our business, operations, industry, financial position or future financial performance include those discussed in Part I, Item 1A "Risk Factors," as well as those discussed in Part II, Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Annual Report on Form 10-K, as well as other factors which may be identified from time to time in our other filings with the Securities and Exchange Commission ("SEC"), or in the documents where such forward-looking statements appear. You should carefully consider that information before you make an investment decision.

You should not place undue reliance on these statements, which speak only as of the date that they were made. Our actual results or experience could differ significantly from those anticipated in the forward-looking statements and from historical results, due to the risks and uncertainties described in this Annual Report on Form 10-K including in "Part I, Item 1A. "Risk Factors," as well as others that we may consider immaterial or do not anticipate at this time. These cautionary statements should be considered in connection with any written or oral forward-looking statements that we may make in the future or may file or furnish with the SEC. We do not undertake any obligation to release publicly any revisions to these forward-looking statements after completion of the filing of this Annual Report on Form 10-K to reflect later events or circumstances or to reflect the occurrence of unanticipated events. All forward-looking statements attributable to us are expressly qualified in their entirety by these cautionary statements.

In addition, with respect to all our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

Summary Risk Factors

An investment in our ordinary shares involves significant risks. You should carefully consider the information set forth under "Risk Factors" before deciding to invest in our ordinary shares. The following is a summary of the principal risks associated with an investment in our ordinary shares:

- We and CSL Behring may be unable to close the transaction contemplated by the CSL Behring Agreement, and any delay in closing the transaction could diminish the anticipated benefits of the transaction or result in increased costs. Failure to close the transaction could adversely impact the market price of our ordinary shares as well as our business and operating results, cash flows and results of operations.
- We may encounter substantial delays in, and impediments to the progress of our clinical trials or fail to demonstrate the safety and efficacy of our product candidates, and our clinical trials for AMT-061 are currently on clinical hold and could remain on clinical hold indefinitely.
- Our business and operations have been, and may continue to be, materially and adversely affected by the ongoing COVID-19 pandemic.
- We may not be successful in our efforts to use our gene therapy technology platform to build a pipeline of additional product candidates.
- We may not be successful in our efforts to in-license or acquire product candidates that align with our research and development strategy.
- Our manufacturing facility is subject to significant government regulations and approvals. If we fail to comply with these regulations or to maintain these approvals our business could be materially harmed.
- Our resources might be adversely affected if we are unable to meet our product development and supply needs and obligations, including our ability to complete the validation of our existing manufacturing processes as well as to develop larger scale manufacturing processes, which could adversely affect our ability to sufficiently meet our future production needs or regulatory filing timelines.
- Our resources might be adversely affected if we are unable to meet our product supply needs and obligations.
- We cannot predict when or if we will obtain marketing approval to commercialize a product candidate.
- We are exposed to a number of external factors such as competition, insurance coverage of and pricing and reimbursement for our product candidates that may adversely affect our product revenue and that may cause our business to suffer.
- We rely on licenses of intellectual property from third parties, and such licenses may not provide adequate rights or may not be available in the future on commercially reasonable terms or at all, and our licensors may be unable to obtain and maintain patent protection for the technology or products that we license from them.
- If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection is not sufficiently broad, our ability to successfully commercialize our products may be impaired.
- Our reliance on third parties may require us to share our trade secrets, which could increase the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.
- We will likely need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product development efforts or other operations which could have a material adverse effect on our business, financial condition, results of operations, and cash flows.
- Our relationships with customers and third-party payers will be subject to applicable anti-kickback, anti-bribery, fraud and abuse and other laws and regulations, which, if we are found in violation thereof, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.
- We are subject to laws governing data protection in the different jurisdictions in which we operate. The implementation of such data protection regimes is complex, and should we fail to fully comply, we may be subject to penalties that may have an adverse effect on our business, financial condition, and results of operations.

- Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.
- If we fail to maintain an effective system of internal controls, we may be unable to accurately report our results of operations or prevent fraud or fail to meet our reporting obligations, and investor confidence and the market price of our ordinary shares may be materially and adversely affected.

Part I

Unless the context requires otherwise, references in this report to "uniQure," "Company," "we," "us" and "our" and similar designations refer to uniQure N.V. and our subsidiaries.

Item 1. Business.

Overview

We are a leader in the field of gene therapy, seeking to develop single treatments with potentially curative results for patients suffering from genetic and other devastating diseases. We are advancing a focused pipeline of innovative gene therapies, including product candidates for the treatment of hemophilia B, which we intend to license to CSL Behring pursuant to the CSL Behring Agreement (as defined below), and Huntington's disease. We believe our validated technology platform and manufacturing capabilities provide us distinct competitive advantages, including the potential to reduce development risk, cost, and time to market. We produce our Adeno-associated virus ("AAV") -based gene therapies in our own facilities with a proprietary, commercial-scale, current good manufacturing practices ("cGMP")-compliant, manufacturing process. We believe our Lexington, Massachusetts-based facility is one of the world's most versatile gene therapy manufacturing facilities.

Key events

CSL Behring commercialization and license agreement

On June 24, 2020, uniQure biopharma B.V., a wholly-owned subsidiary of uniQure N.V., entered into a commercialization and license agreement (as amended, the "CSL Behring Agreement") with CSL Behring LLC ("CSL Behring") pursuant to which CSL Behring will receive exclusive global rights to etranacogene dezaparvovec, our investigational gene therapy for patients with hemophilia B (the "Product").

Under the terms of the CSL Behring Agreement, we will receive a $450.0 million upfront cash payment upon the closing of the CSL Behring Agreement and be eligible to receive up to $1.6 billion in additional payments based on regulatory and commercial milestones. The CSL Behring agreement also provides that we will be eligible to receive tiered double-digit royalties in a range of up to a low-twenties percent of net sales of the Product based on sales thresholds.

Pursuant to the CSL Behring Agreement, we will be responsible for the completion of the HOPE-B clinical trial, manufacturing process validation, and the manufacturing supply of the Product until such time that these capabilities may be transferred to CSL Behring or its designated contract manufacturing organization. Concurrently with the execution of the CSL Behring Agreement, we and CSL Behring entered into a development and commercial supply agreement, pursuant to which, among other things, we will supply the Product to CSL Behring at an agreed-upon price. Clinical development and regulatory activities performed by us pursuant to the CSL Behring Agreement will be reimbursed by CSL Behring. CSL Behring will be responsible for global regulatory submissions and commercialization requirements for the Product.

Other than under the CSL Behring Agreement, neither we nor CSL Behring may perform any clinical trials, with the exception of trials required to extend the label or gain marketing authorization outside the United States or the European Union, for any gene therapy product, gene-editing product, or any other product comprising an AAV vector to conduct nucleotide transfer (including deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA")) for the treatment, prevention, or cure of hemophilia B for a period commencing on June 24, 2020 and continuing for a period of four years following the first commercial sale of the Product in the United States, and neither we nor CSL Behring may commercialize such a product for a period commencing as of June 24, 2020 and continuing for a period of seven years following the first commercial sale of the Product in the United States. This exclusivity commitment would not bind an acquirer of us that owns or controls such a product so long as certain precautions are followed to ensure that CSL Behring's confidential information and our proprietary technology related to the Product are not used or accessed by personnel of such acquirer who are developing or commercializing such competing product.

Unless earlier terminated as described below, the CSL Behring Agreement will continue on a country-by-country basis until expiration of the royalty term in a country. The royalty term expires in a country on the later of (a) 15 years after the first commercial sale of the Product in such country, (b) expiration of regulatory exclusivity for the Product in such country and (c) expiration of all valid claims of specific licensed patents covering the Product in such country. Either we or CSL Behring may terminate the CSL Behring Agreement for the other party's material breach if such breach is not cured within a specified cure period. In addition, if CSL Behring fails to commercialize the Product in any of a group of major countries for an extended period of time following the first regulatory approval of the Product in any of such group of countries (other than due to certain specified reasons) and such failure has not been cured within a specified cure period, then we may terminate the CSL Behring Agreement. CSL Behring may also terminate the CSL Behring Agreement for convenience.

The effectiveness of the transactions contemplated by the CSL Behring Agreement is contingent on completion of review under antitrust laws in the United States, Australia, and the United Kingdom, and certain provisions of the CSL Behring Agreement will not become effective until after we receive all such regulatory approvals.

On November 11, 2020, the Australian Competition and Consumer Commission ("ACCC") determined, pursuant to section 50 of the Competition and Consumer Act 2010 of Australia, that it will not intervene in the CSL Behring Agreement. Thus, the ACCC has completed its review of the CSL Behring Agreement, and the transactions contemplated by the CSL Behring Agreement may close from the perspective of the Australian competition authority.

On November 24, 2020, the Competition and Markets Authority in the United Kingdom (the "CMA") adopted a decision not to refer the CSL Behring Agreement for proceedings under section 33 of the Enterprise Act 2002 of the United Kingdom. The decision was made public by the CMA on January 6, 2021. Thus, the CMA has completed its review of the CSL Behring Agreement, and the transactions contemplated by the CSL Behring Agreement may close from the perspective of the United Kingdom competition authority.

On December 3, 2020, we and CSL Behring filed a premerger notification and report form under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (the "HSR Act"). On January 4, 2021, the United States Federal Trade Commission ("FTC") issued to us a request for additional information and documentary material (a "Second Request") under the HSR Act. The FTC similarly issued a Second Request to CSL Behring also with respect to the antitrust review of the CSL Behring Agreement. The effect of the Second Request is to extend the waiting period imposed under the HSR Act until 30 days after all parties to the CSL Behring Agreement have substantially complied with the requests unless the waiting period is terminated earlier by the FTC or voluntarily extended by the parties. We do not believe that the FTC will determine that the consummation of the transaction will result in a violation of the HSR Act. However, there can be no assurance as to the outcome of the Second Request.

Closing of the transaction is expected to materially impact our profitability and cash flows. Receipt of the $450.0 million payment due on closing would extend the funding of our operations into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules Capital Inc. ("Hercules") under our term loan facility by 2023). However, we expect to continue to incur losses and to generate negative cash flows beyond the fiscal year in which we would close the transaction.

Hemophilia B program – Etranacogene dezaparvovec (AMT-061)

Etranacogene dezaparvovec is our lead gene therapy candidate and includes an Adeno-associated virus ("AAV") serotype 5 (together "AAV-5") vector incorporating the functional human Factor IX ("FIX") Padua variant. We are currently conducting a pivotal study in patients with severe and moderately-severe hemophilia B.

In August 2018, we initiated a Phase IIb dose-confirmation study of etranacogene dezaparvovec and in September 2018, we completed the dosing for that study. In February, May, July, and December 2019, and in December 2020, we presented updated data from the Phase IIb dose-confirmation study of etranacogene dezaparvovec. The most recent data that we announced from the Phase IIb study of etranacogene dezaparvovec show that all three patients experienced increasing and sustained FIX levels after a one-time administration of etranacogene dezaparvovec. Mean FIX activity was 44.2% of normal two years after administration, exceeding threshold FIX levels generally considered sufficient to significantly reduce the risk of bleeding events. The first patient achieved FIX activity of 44.7% of normal, the second patient was 51.6% of normal and the third patient was 36.3% of normal. The second and third patients had previously screen-failed and were excluded from another gene therapy study due to pre-existing neutralizing antibodies to a different AAV vector. At two years after dosing, two of the three participants remain free from bleeds and use of FIX replacement therapy. A single bleed has been reported in one participant, who has used a total of two FIX infusions (excluding surgery). All patients have remained free of prophylaxis in the two years since receiving etranacogene dezaparvovec.

In June 2018, we initiated the six-month lead-in period of our Phase III HOPE-B pivotal trial of etranacogene dezaparvovec (the "HOPE-B trial"). The HOPE-B trial is a multinational, multi-center, open-label, single-arm study to evaluate the safety and efficacy of etranacogene dezaparvovec. After the six-month lead-in period, patients received a single intravenous administration of etranacogene dezaparvovec. Patients enrolled in the HOPE-B trial were tested for the presence of pre-existing neutralizing antibodies to AAV5 but not excluded from the trial based on their titers.

The primary endpoints of the study are based on the FIX activity level achieved following the administration of etranacogene dezaparvovec after 26 weeks and 52 weeks after dosing as well as annualized bleed rates during the 52 weeks after dosing.

In March 2020, we completed dosing of the 54 patients in the HOPE-B trial. The targeted number of patients to be dosed per the clinical trial protocol was 50. As set forth below, we have implemented and continue to implement various measures to allow us to closely monitor the trial within the guidance provided by the U.S. Food and Drug Administration ("FDA") regarding the impact of the COVID-19 coronavirus pandemic ("COVID-19") to minimize any risk or disruption in patient follow-up visits.

In December 2020, we announced top-line data from the HOPE-B trial. The 26-week follow-up date from the trial showed that FIX activity in the 54 patients increased after dosing from ≤ 2% to a mean of 37.2% at 26 weeks, meeting a first primary endpoint of the HOPE-B trial. No correlation between pre-existing neutralizing antibodies and FIX activity was found in patients with neutralizing antibody titers up to 678.2, a range expected to include more than 95% of the general population; one patient with a neutralizing antibody titer of 3,212.3 did not show an increase in FIX activity. Less than 1% of the general population is expected to have neutralizing antibody titers of greater than 3,000.

During the 26-week period after dosing, 15 patients (28%) reported a total of 21 bleeding events, representing a reduction of 83% compared to the 123 bleeding events reported by 38 patients (70%) during the observational lead-in phase of the trial. Total bleeds include any bleeding event reported after the treatment of etranacogene dezaparvovec, including spontaneous, traumatic, and those associated with unrelated medical procedures, whether or not FIX treatment was required. Of the total bleeding events reported during the 26-week period after dosing, only three were classified as spontaneous bleeds requiring treatment, representing a reduction of 92% compared to the 37 such bleeding events reported during the observational lead-in phase. Mean annualized usage of FIX replacement therapy, a secondary endpoint in the clinical trial, declined by 96% during the 26-week period after dosing compared to the observational lead-in phase. Etranacogene dezaparvovec was generally well-tolerated. As of the November 2020 cut-off date, most adverse events were classified as mild (81.5%). The most common events included transaminase elevation treated with steroids per protocol (9 patients; 17%), infusion-related reactions (7 patients; 13%), headache (7 patients; 13%) and influenza-like symptoms (7 patients; 13%). Liver enzyme elevations resolved with a tapering course of corticosteroids and FIX activity remained in the mild range in the steroid treated patients. No relationship between safety and neutralizing antibody titers was observed. Based on interactions with the FDA and the European Medicines Agency ("EMA"), we plan to incorporate FIX activity and bleeding rates at 52 weeks as additional co-primary endpoints in the study.

On December 21, 2020, our clinical trials of etranacogene dezaparvovec, including our HOPE-B trial, were placed on clinical hold by the FDA. The clinical hold was initiated following the submission of a safety report in mid-December relating to a possibly related serious adverse event associated with a preliminary diagnosis of hepatocellular carcinoma ("HCC"), a form of liver cancer, in one patient in the HOPE-B trial that was treated with etranacogene dezaparvovec in October 2019. The patient has multiple risk factors associated with HCC, including a twenty-five-year history of hepatitis C ("HCV"), hepatitis B virus ("HBV"), evidence of non-alcoholic fatty liver disease and advanced age. Chronic infections with hepatitis B and C have been associated with approximately 80% of HCC cases.

The liver lesion was detected during a routine abdominal ultrasound conducted as part of the required study assessments in patients at one-year post dosing. A surgical resection of the lesion has occurred, and an analysis of the tissue samples was initiated in early 2021. On February 19, 2021, we reported initial results from this analysis to the FDA in accordance with pharmacovigilance requirements. We are gathering final data from these molecular analyses and will be preparing a detailed response to the FDA's clinical hold questions regarding this event. Currently, we do not have adequate data to determine a possible causal relationship, especially in the context of the other known risk factors. We currently do not anticipate any impact on our regulatory submission timelines, including the filing of a BLA.

No other cases of HCC have been reported in our clinical trials conducted in more than 67 patients in hemophilia B, with some patients dosed more than 5 years ago.

Etranacogene dezaparvovec has been granted Breakthrough Therapy Designation by the FDA and access to the current priority medicines ("PRIME") initiative by the EMA.

Huntington's disease program (AMT-130)

AMT-130 is our novel gene therapy candidate for the treatment of Huntington's disease. AMT-130 utilizes our proprietary, gene-silencing miQURE platform and incorporates an AAV vector carrying an miRNA specifically designed to silence the huntingtin gene and the potentially highly toxic exon 1 protein fragment. AMT-130 has received orphan drug and Fast Track designations from the FDA and Orphan Medicinal Product Designation from the EMA.

In June 2020, we announced the completion of the first two patient procedures in the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease. These procedures occurred after a postponement that resulted from the COVID-19 pandemic and the associated states of emergency declarations in the United States. The Phase I/II protocol is a randomized, imitation surgery-controlled, double-blinded study conducted at three surgical sites, and multiple referring, non-surgical sites in the U.S. The primary objective of the study is to evaluate the safety, tolerability, and efficacy of AMT-130 at two doses.

On September 25, 2020, we announced that the independent Data Safety Monitoring Board ("DSMB") overseeing the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease had met and reviewed 90-day safety data from the first two patients enrolled in the trial. No significant safety concerns were noted to prevent further dosing.

On October 13, 2020, we announced the completion of the third and fourth patient procedures in the Phase I/II clinical trial.

On February 8, 2021, we announced that the DSMB had met and reviewed the six-month safety data from the first two enrolled patients and the 90-day safety data from the next two enrolled patients in the study. No significant safety concerns were noted to prevent further dosing, and the final six patients in the first cohort are now cleared for enrollment.

BMS collaboration

We and Bristol-Myers Squibb ("BMS") entered into a collaboration and license agreement in May 2015 ("BMS CLA"). BMS had initially designated four Collaboration Targets in 2015 and in accordance with the terms of the BMS CLA could have designated a fifth to tenth Collaboration Target.

In February 2019, BMS requested a one-year extension of the initial research term. In April 2019, following an assessment of the progress of this collaboration and our expanding proprietary programs, we notified BMS that we did not intend to agree to an extension of the initial research term. Accordingly, the initial four-year research term under the collaboration terminated on May 21, 2019.

On December 1, 2020, we and BMS amended the BMS CLA ("amended BMS CLA"). Following the amendment BMS is no longer entitled to designate a fifth to tenth Collaboration Target and as such we are no longer entitled to receive an aggregate $16.5 million in target designation payments for research, development, and regulatory milestone payments related to the fifth and tenth Collaboration Targets. For a period of one-year from the effective date of the amended BMS CLA, BMS may replace up to two of the four active Collaboration Targets with two new targets in the field of cardiovascular disease. We continue to be entitled to receive up to $217.0 million for each of the four Collaboration Targets if defined milestones are achieved, as well as royalties on net sales associated with any Collaboration Target. On December 17, 2020, BMS designated one of the four Collaboration Targets as a candidate to advance into IND-enabling studies entitling us to receive a $4.4 million research milestone payment. We recorded the $4.4 million as License Revenue in the twelve-month period ended December 31, 2020.

The amended BMS CLA does not extend the initial research term. BMS may place purchase orders to provide limited services primarily related to analytical and development efforts in respect of the four Collaboration Targets. BMS may request such services for a period not to exceed the earlier of (i) the completion of all activities under a Research Plan and (ii) either (A) three years after the last replacement target has been designated by BMS during the one-year replacement period following the amended BMS CLA effective date or (B) three years if no replacement targets are designated during this one-year period and BMS continues to reimburse us for these services.

For as long as any of the four Collaboration Targets are being advanced, BMS may place a purchase order to be supplied with research, clinical and commercial supplies. Subject to the terms of the amended BMS CLA, BMS has the right to terminate the research, clinical and commercial supply relationships, and has certain remedies for failures of supply, up to and including technology transfer for any such failure that otherwise cannot be reasonably resolved. Both we and BMS may agree to a technology transfer of manufacturing capabilities pursuant to the terms of the amended BMS CLA.

We have agreed to certain restrictions on our ability to work independently of the collaboration, either directly or indirectly through any affiliate or third party, on certain programs that would be competitive with a Collaboration Target. We have agreed to indication exclusivity for the current four Collaboration Targets. BMS may add or change the exclusive indications in the process of replacing Collaboration Targets as described above. We can opt out of the indication exclusivity by giving up certain economic rights under the amended BMS CLA for each such indication that is affected by us opting out. If we opt out of an exclusive indication, we could pursue other targets for such indication other than a Collaboration Target.

The amended BMS CLA also terminated two warrants to increase BMS ownership in the Company up to 19.9% through purchasing a specific number of our ordinary shares following the designation of a seventh, and a tenth Collaboration Target, respectively. We and BMS agreed that upon the consummation of a change of control transaction of uniQure that occurs prior to the earlier of (i) December 1, 2026 and (ii) BMS' delivery of a target cessation notice for all four Collaboration Targets, uniQure (or its third party acquirer) shall pay to BMS a one-time, non-refundable, non-creditable cash payment of $70.0 million, provided that (x) if $70.0 million is greater than five percent of the net proceeds (as contractually defined) from such change of control transaction, the payment shall be an amount equal to five percent of such net proceeds, and (y) if $70.0 million is less than one percent of such net proceeds, the change of control payment shall be an amount equal to one percent of such net proceeds. We have not consummated any change of control transaction as of December 31, 2020 that would obligate us to make a payment to BMS.

The amended BMS CLA did not change any of the provisions of the Investor Agreement with BMS that we entered into in 2015. We have granted BMS certain registration rights that allow BMS to require us to register our securities beneficially held by BMS under the U.S. Securities Exchange Act of 1934, as amended ("Exchange Act"). BMS may make up to two such demands for us to register the shares, provided that we may deny such demand if (i) the market value of the shares to be registered is less than $10.0 million (provided however, if BMS holds less than $10.0 million worth of our shares, we must comply with their demand for registration), (ii) we certify to BMS that we plan to effect a registration within 120 days of their demand or we are engaged in a transaction that would be required to be disclosed in a registration statement and that is not reasonably practicable to be disclosed at that time, or (iii) we have already effected one registration statement within the twelve months preceding BMS's demand for registration. In addition, independent of their demand registration rights, upon the occurrence of certain events, we must also provide BMS the opportunity to include their ordinary shares in any registration statement that we effect.

We also continue to grant BMS certain information rights under the Investor Agreement, although these requirements may be satisfied by our public filings required by U.S. securities laws.

BMS also continues to be subject to a lock up pursuant to the Investor Agreement for as long as BMS holds more than 4.9% of our ordinary shares (as of December 31, 2020 BMS holds 5.3%). Without our prior consent, BMS may not sell or dispose any of its current ordinary shares.

The Investor Agreement also continues to require BMS to vote all of our ordinary shares it beneficially holds in favor of all items on the agenda for the relevant general meeting of shareholders of our company as proposed on behalf of our company, unless, in the context of a change of control or similar transaction, BMS has itself made an offer to our company or our board in connection with the transaction that is the subject of the vote, in which case it is free to vote its shares at its discretion. This voting provision will terminate upon the later of the date on which BMS no longer beneficially owns at least 4.9% of our outstanding ordinary shares, the closing of a transaction that provides BMS exclusive and absolute discretion to vote our shares it beneficially holds, or the termination of the amended BMS CLA for breach by us.

Term loan facility

As of December 31, 2020, a $35.0 million term loan was outstanding in accordance with the Second Amended and Restated Loan and Security Agreement ("2018 Amended Facility") between us and Hercules.

On January 29, 2021 we and Hercules entered into amendments to the 2018 Amended Facility (the "2021 Amended Facility"). Pursuant to the 2021 Amended Facility, Hercules agreed to make additional term loans in the maximum aggregate amount of $100.0 million (the "2021 Term Loan"), increasing the aggregate principal amount of the term loan facility from $35.0 million to up to $135.0 million. On January 29, 2021 we drew down $35.0 million of the 2021 Term Loan. We may draw down the remaining $65.0 million under the 2021 Term Loan in a series of one or more advances of not less than $20.0 million each until December 15, 2021. Advances under the 2021 Term Loan bear interest at a rate equal to the greater of (i) 8.25% or (ii) 8.25% plus the prime rate, less 3.25% per annum. The principal balance and all accrued but unpaid interest on advances under the 2021 Term Loan is due on June 1, 2023, which date may be extended by us by up to two twelve-month periods. Advances under the 2021 Term Loan may not be prepaid until six-months after the Closing Date, following which we may prepay all such advances without charge.

In addition to the 2021 Term Loan, the amendment also extends the interest only payment period of the previously funded $35.0 million term loan from January 1, 2022 to June l, 2023.

COVID-19 measures

The coronavirus disease ("COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 ("Sars-CoV 2 virus) was characterized as a pandemic by the World Health Organization ("WHO") on March 11, 2020. During late 2020 various, potentially more infectious, variants of the Sars-CoV 2 virus causing COVID-19 were identified.

Starting March 2020, we implemented measures to address the impact of COVID-19 on our business. We mandated a work-from-home policy for all non-essential employees at our Amsterdam and Lexington facilities when the pandemic began. We implemented a series of protocols governing the operations of our Lexington facility to comply with the requirements of the various orders and guidance from the Commonwealth of Massachusetts and other related orders, guidance, laws, and regulations. We supported our employees in setting up a healthy and efficient remote working environment. In conjunction with implementing this policy, we accelerated the roll-out of several information technology security measures, such as dual factor authentication, to address the increased risks to which we might be exposed as a result of remote working conditions. In addition, we conducted awareness training around cybersecurity for critical functions involved in making payments to vendors such as finance and supply chain. We continue to monitor local government rules and recommendations and office protocols will be aligned with these rules and recommendations.

We conduct frequent status video-meetings of local management at our two sites as well as leadership-team video meetings to implement these measures and to monitor the evolving situation. In addition, we inform our employees through periodic newsletters and have organized virtual local and global townhalls to share information and provide direction and support to our employees.

We started to reopen the Amsterdam and Lexington facilities in phases, in line with the reopening plans that are prescribed by the local government. Between June 1, 2020 until September 29, 2020, we encouraged our Amsterdam employees to work a minimum of two days per week from the office, and approximately 50% of local staff worked on site during that period. As of September 29, 2020, we reinstated the mandatory work-from-home policy that was initiated in March in Amsterdam to align with the updated Dutch government's measures. Employees based in Amsterdam who cannot perform their duties outside of our Amsterdam facility will continue to work at our Amsterdam facility. We adapted to operate our laboratories at our Amsterdam site to comply with social distancing rules and to ensure the health and wellbeing of our employees under the current circumstances. All other employees in Amsterdam will work from home through at least the end of August 2021, partly in conjunction with the ongoing expansion of our laboratory space.

As a biopharma research and development company, we were deemed to provide essential services under the "stay at home" advisory that was issued by the Governor of Massachusetts on March 23, 2020 and we therefore have maintained our manufacturing operations at our Lexington site. To ensure adequate social distancing in our Lexington facility, our COVID-19 protocols generally have limited occupancy to numbers below those allowed by the Massachusetts COVID-19 guidelines. In our Lexington facility, we currently have implemented an occupancy limitation of approximately 25%. Our employees that cannot perform their duties outside of our Lexington facility continue to work at our Lexington facility. All other employees are required to work remotely to the extent possible through at least the end of the second quarter of 2021. Our actual occupancy at the Lexington facility has been less than approximately 25% of our permitted occupancy during all phases of the Massachusetts reopening plan. We have also implemented a mandatory COVID-19 PCR testing protocol effective February 11, 2021 that requires employees to have tested negative for COVID-19 prior to entering the Lexington facility.

We have adapted our ongoing clinical research activities based on the directions and flexibility provided by the "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" issued on March 18, 2020 and updated throughout the pandemic to minimize any risk, disruption, or delay in either patient dosing or follow-up visits. These procedures occurred after a postponement that resulted from the COVID-19 pandemic and the associated states of emergency declarations in the United States.

The broader implications of COVID-19 on our results of operations and overall financial performance remain uncertain. The COVID-19 pandemic and its adverse effects have become more prevalent in the locations where we, and our third-party business partners conduct business. While we have experienced disruptions in our operations as a result of COVID-19, we are adapting to the current environment to minimize the effect to our business. However, we may experience more pronounced disruptions in our operations in the future.

Organization

On September 14, 2020, we appointed Ricardo Dolmetsch, Ph.D. as President, Research and Development. Dr. Dolmetsch succeeded Sander van Deventer, M.D., Ph.D., our former Executive Vice President, Research and Product Development. On October 14, 2020, our Chief Medical Officer, Robert Gut, M.D., Ph.D., resigned to allow him to return as a non-executive director on our Board of Directors. Dr. Gut was appointed to our Board of Directors as a non-executive director at an extraordinary meeting of shareholders on December 1, 2020.

On June 17, 2020, our shareholders voted to approve the appointment of Leonard E. Post, Ph.D. as a non-executive director of the Board of Directors. Dr. Post replaced Dr. David Schaffer, whose term as a non-executive director of the Board of Directors ended on the same date. Dr. Post has also assumed the role of chair of our Research & Development Committee of the Board of Directors.

Our Mission and Strategy

Our mission is to build an industry-leading, fully integrated, and global company that leverages its validated technology and manufacturing platform to deliver transformative gene therapy products to patients with serious unmet medical needs.

Our strategy to achieve this mission is to:

Advance the development of etranacogene dezaparvovec (AMT-061), a potentially best-in-class treatment of hemophilia B. Etranacogene dezaparvovec combines the potential advantages of AAV5 with an enhanced Padua-FIX transgene, and may provide optimized clinical and tolerability benefits to all, or nearly all patients with hemophilia B. In March 2020, we completed dosing of 54 patients in our Phase III HOPE-B pivotal study.

Maintain our leadership position in commercial-scale AAV manufacturing. We have established cGMP, commercial-scale manufacturing capabilities for AAV-based gene therapies in our state-of-the-art Lexington, Massachusetts facility. We believe the modularity of our platform provides us with distinct advantages, including the potential for reduced development risk and faster times to market.

Build a pipeline of gene therapy programs focused on rare and orphan diseases targeting liver-directed and central-nervous system ("CNS") diseases. Beyond our lead clinical program for hemophilia B and our Huntington's disease program, we have a pipeline of additional AAV-based gene therapy programs in various stages of preclinical development. We are leveraging our leading technology platform, which includes novel vectors, promoters, and manufacturing capabilities, to develop gene therapies primarily focused on rare, monogenic liver-directed, and CNS disorders as well as cardiovascular diseases.

Leverage the favorable immunogenicity profile of AAV5-based gene therapies to develop multiple products. We have developed extensive experience with our AAV5-based gene therapies, including in five clinical trials in multiple liver-directed and CNS diseases. During these clinical trials, no patient treated with AAV5-based gene therapies experienced a confirmed immune response to the AAV5 capsid or complications associated with T-cell activation. Additionally, the AAV5 capsid has demonstrated a low avidity to pre-existing neutralizing antibodies ("Nab"), which may enable all, or nearly all patients to be eligible for treatment with AAV5-based gene therapies.

Invest in next-generation technologies with the goal of enhancing safety, improving efficacy, and expanding the applicability of gene therapy to patients. We are developing proprietary technologies that have the potential to augment the safety and efficacy of our product candidates and broaden the applicability of our gene therapies to a wider range of diseases and patients. These technologies include (i) miQURE, our one-time administered gene silencing platform, (ii) tailored vectors, promoters, and other enhancers; (iii) optimized delivery and administration techniques; and (iv) novel transgenes. These technologies are developed both in-house by our experienced research team in Amsterdam, the Netherlands, as well as via collaborations with third parties.

Continue to expand our intellectual property portfolio. We have established what we believe is a leading intellectual property portfolio covering various aspects of our technology and programs, including (i) elements of our gene therapy constructs, such as AAV vectors, promoters and transgenes, including the novel Padua-FIX gene we utilize in etranacogene dezaparvovec for hemophilia B; (ii) innovative delivery technologies, such as re-administration of AAV gene therapy; and (iii) proprietary manufacturing processes covering key components of our upstream and downstream capabilities. We expect to continue to expand our intellectual property portfolio by aggressively seeking patent protection for promising aspects of our technology platform and product candidates.

Our Product Candidates

A summary of our key development programs is provided below:

Liver-directed diseases

Hemophilia B (etranacogene dezaparvovec)

Hemophilia B Disease and Market Background

Hemophilia B is a serious and rare inherited disease in males characterized by insufficient blood clotting. The condition can lead to repeated and sometimes life-threatening episodes of external and internal bleeding following accidental trauma or medical interventions. Severe hemophilia is characterized by recurrent episodes of spontaneous joint bleeds that cause long-term damage to the joints resulting in disabling arthropathy. Bleeds may be fatal if they occur in the brain. The deficient blood clotting results from the lack of functional human Factor IX ("hFIX"). Treatment of hemophilia B today consists of prophylactic or on-demand protein replacement therapy, in which one to three times weekly intravenous administrations of plasma-derived or recombinant hFIX are required to prevent bleeding and once daily infusions in case bleeding occurs. Hemophilia B occurs in approximately 1 out of 30,000 live male births.

CSL Behring collaboration

On June 24, 2020, we entered into the CSL Behring Agreement pursuant to which CSL Behring would receive exclusive global rights to etranacogene dezaparvovec. Pursuant to the CSL Behring Agreement, we would be responsible for the completion of the HOPE-B clinical trial, manufacturing process validation, and the manufacturing supply of etranacogene dezaparvovec until such time that these capabilities may be transferred to CSL Behring or its designated contract manufacturing organization. Concurrently with the execution of the CSL Behring Agreement we and CSL Behring entered into a development and commercial supply agreement, pursuant to which, among other things, we would supply etranacogene dezaparvovec to CSL Behring at an agreed-upon price. Clinical development and regulatory activities performed by us pursuant to the CSL Behring Agreement would be reimbursed by CSL Behring. CSL Behring would be responsible for global regulatory submissions and commercialization requirements for etranacogene dezaparvovec. The CSL Behring Agreement continues to be subject to antitrust review in the U.S. and as such is not yet effective.

Our Development of etranacogene dezaparvovec for Hemophilia B

We are currently developing etranacogene dezaparvovec, a gene therapy for patients with hemophilia B that is designed to restore FIX activity, an essential protein for blood clotting. Etranacogene dezaparvovec includes an AAV5 vector incorporating the FIX-Padua variant ("FIX-Padua"). Etranacogene dezaparvovec is identical in structure to our first-generation hemophilia B product candidate, AMT-060, apart from two nucleotide substitutions in the coding sequence for FIX. The FIX-Padua variant expresses a protein with a single amino acid substitution that has been reported in multiple preclinical and nonclinical studies to provide an approximate eight-to nine-fold increase in FIX activity compared to the wild-type FIX protein, which was incorporated in AMT-060. All other critical quality attributes of AMT-061 are expected to be comparable to those of AMT-060, as AMT-061 utilizes the same AAV5 capsid and proprietary insect cell-based manufacturing platform.

Etranacogene dezaparvovec is intended to be delivered by intravenous ("IV")-infusion, without immunosuppressant therapy, through the peripheral vein in a single treatment session for approximately 30 minutes.

Our goal for etranacogene dezaparvovec is to develop a gene therapy with the following profile:

- long-term safety, including a favorable immunogenicity profile;
- predictable, sustained and potentially curative increases in FIX activity;
- significant reductions in both bleeding rates and the need for FIX replacement therapy; and
- broad patient eligibility, including the potential to treat all or nearly all patients with hemophilia B.

AAV5-based gene therapies have been used in a multitude of clinical trials, including five clinical trials conducted by us in patients with hemophilia B and other disorders. No patient treated in clinical trials with our AAV5-based gene therapies has experienced any confirmed, cytotoxic T-cell-mediated immune response to the capsid. An independent clinical trial has demonstrated that AAV5 has the lowest prevalence of pre-existing neutralizing antibodies compared to other AAV vectors. Data from our clinical, preclinical, and nonclinical studies suggest that all, or nearly all patients may be eligible for treatment with etranacogene dezaparvovec.

The FDA has agreed that etranacogene dezaparvovec will fall under the existing Breakthrough Therapy Designation and IND for AMT-060, and the EMA has also agreed that etranacogene dezaparvovec will fall under the PRIME designation.

In June 2018, we initiated our Phase III HOPE-B pivotal trial of etranacogene dezaparvovec. The trial is a multinational, multi-center, open-label, single-arm study to evaluate the safety and efficacy of etranacogene dezaparvovec.

In March 2020, we completed dosing of the 54 patients in the HOPE-B trial. The targeted number of patients to be dosed per the clinical trial protocol was 50. As set forth previously, we have implemented and continue to implement various measures to allow us to closely monitor the trial within the guidance provided by the FDA regarding the impact of the COVID-19 coronavirus pandemic to minimize any risk or disruption in patient follow-up visits. The adult hemophilia B patients, who were classified as severe or moderately severe, were enrolled in a six-month observational period prior to dosing during which time they continued to use their current standard of care to establish a baseline control. After the six-month lead-in period, patients received a single IV-administration of etranacogene dezaparvovec. Patients enrolled in the HOPE-B trial were tested for the presence of pre-existing neutralizing antibodies to AAV5 but not excluded from the trial based on their titers. The primary endpoints of the study are based on the FIX activity level achieved following the administration of etranacogene dezaparvovec after 26 weeks and 52 weeks after dosing as well as annualized bleed rates during the 52 weeks after dosing.

In December 2020, we announced top-line data from the HOPE-B trial. The 26-week follow-up date from the trial showed that FIX activity in the 54 patients increased after dosing from $\leq$ 2% to a mean of 37.2% at 26 weeks, meeting a first primary endpoint of the HOPE-B trial. No correlation between pre-existing neutralizing antibodies and FIX activity was found in patients with neutralizing antibody titers up to 678.2, a range expected to include more than 95% of the general population; one patient with a neutralizing antibody titer of 3,212.3 did not show an increase in FIX activity. Less than 1% of the general population is expected to have neutralizing antibody titers of greater than 3,000.

During the 26-week period after dosing, 15 patients (28%) reported a total of 21 bleeding events, representing a reduction of 83% compared to the 123 bleeding events reported by 38 patients (70%) during the observational lead-in phase of the trial. Total bleeds include any bleeding event reported after the treatment of etranacogene dezaparvovec, including spontaneous, traumatic, and those associated with unrelated medical procedures, whether or not FIX treatment was required. Of the total bleeding events reported during the 26-week period after dosing, only three were classified as spontaneous bleeds requiring treatment, representing a reduction of 92% compared to the 37 such bleeding events reported during the observational lead-in phase. Mean annualized usage of FIX replacement therapy, a secondary endpoint in the clinical trial, declined by 96% during the 26-week period after dosing compared to the observational lead-in phase. Etranacogene dezaparvovec was generally well-tolerated. As of the November 2020 cut-off date, most adverse events were classified as mild (81.5%). The most common events included transaminase elevation treated with steroids per protocol (9 patients; 17%), infusion-related reactions (7 patients; 13%), headache (7 patients; 13%) and influenza-like symptoms (7 patients; 13%). Liver enzyme elevations resolved with a tapering course of corticosteroids and FIX activity remained in the mild range in the steroid treated patients. No relationship between safety and neutralizing antibody titers was observed. Based on interactions with the FDA and the EMA, we plan to incorporate FIX activity and bleeding rates at 52 weeks as additional co-primary endpoints in the study.

On December 21, 2020, our clinical trials of etranacogene dezaparvovec, including our HOPE-B trial were placed on clinical hold by the FDA. The clinical hold was initiated following the submission of a safety report in mid-December relating to a possibly related serious adverse event associated with a preliminary diagnosis of HCC, a form of liver cancer, in one patient in the HOPE-B trial that was treated with etranacogene dezaparvovec in October 2019. The patient has multiple risk factors associated with HCC, including a twenty-five-year history of HCV, HBV, evidence of non-alcoholic fatty liver disease and advanced age. Chronic infections with hepatitis B and C have been associated with approximately 80% of HCC cases.

The liver lesion was detected during a routine abdominal ultrasound conducted as part of the required study assessments in patients at one-year post dosing. A surgical resection of the lesion has occurred, and an analysis of the tissue samples was initiated in early 2021. On February 19, 2021, we reported initial results from this analysis to the FDA in accordance with pharmacovigilance requirements. We are gathering final data from these molecular analyses and will be preparing a detailed response to the FDA's clinical hold questions regarding this event. Currently, we do not have adequate data to determine a possible causal relationship, especially in the context of the other known risk factors. We currently do not anticipate any impact on our regulatory submission timelines, including the filing of a BLA.

No other cases of HCC have been reported in our clinical trials conducted in more than 67 patients in hemophilia B, with some patients dosed more than 5 years ago.

In September 2018, we completed the dosing of a Phase IIb dose-confirmation study of etranacogene dezaparvovec. The Phase IIb study is an open-label, single-dose, single-arm, multi-center trial being conducted in the United States. The objective of the study was to evaluate the safety and tolerability of etranacogene dezaparvovec and confirm the dose based on FIX activity at six weeks after administration. Three patients with severe hemophilia were enrolled in this study and received a single intravenous infusion of $2x10^{13}$ genome copies per kilogram ("gc/kg"). Patients were evaluated for the presence of pre-existing neutralizing antibodies to AAV5 but were not excluded from the trial on this basis. We have followed the patients for more than two years to assess FIX activity, bleeding rates and usage of FIX replacement therapy, and will monitor the three patients for a total of five years to evaluate the safety of etranacogene dezaparvovec.

In December 2018, the study's Data Monitoring Committee evaluated initial data from the Phase IIb study and confirmed the dose of $2x10^{13}$ gc/kg for the Phase III pivotal trial.

In February, May, July, and December 2019, and in December 2020, we presented updated data from the Phase IIb dose-confirmation study of etranacogene dezaparvovec. The most recent data that we announced in December 2020 from the Phase IIb study of etranacogene dezaparvovec show that all three patients experienced increasing and sustained FIX levels after a one-time administration of etranacogene dezaparvovec. Mean FIX activity was 44.2% of normal two years after administration, exceeding threshold FIX levels generally considered sufficient to significantly reduce the risk of bleeding events. The first patient achieved FIX activity of 44.7% of normal, the second patient was 51.6% of normal and the third patient was 36.3% of normal. The second and third patients had previously screen-failed and were excluded from another gene therapy study due to pre-existing neutralizing antibodies to a different AAV vector. At two years after dosing, two of the three participants remain free from bleeds and use of FIX replacement therapy. A single bleed has been reported in one participant, who has used a total of two FIX infusions (excluding surgery). All patients have remained free of prophylaxis in the two years since receiving etranacogene dezaparvovec.

Intellectual Property for etranacogene dezaparvovec

In 2017, we acquired intellectual property from Professor Paolo Simioni ("Dr. Simioni"), a hemophilia expert at the University of Padua, Italy. The intellectual property includes U.S. Patent Number 9,249,405, which covers compositions of FIX-Padua nucleic acids and polypeptides (proteins), as well as their therapeutic uses.

On May 29, 2018, the U.S. Patent and Trademark Office ("USPTO") granted us a second patent, U.S. Patent Number 9,982,248, which covers methods of treating coagulopathies (bleeding disorders), including hemophilia B, using AAV-based gene therapy with nucleic acid encoding the hyperactive FIX Padua variant. The FIX Padua variant is a FIX protein carrying a leucine at the R338 position, often called the "FIX-Padua" or "Padua mutant".

On November 5, 2019, the USPTO granted us a third patent, U.S. Patent Number 10,465,180, which covers any AAV comprising a nucleic acid encoding a FIX-Padua protein, and promoter sequences, transcription termination and control elements. The claims also cover FIX-Padua variants with at least 70% sequence identity to FIX-R338L.

In addition to the U.S. patents, on February 20, 2018, the Canadian Intellectual Property Office granted Patent Number 2,737,094, which covers FIX-Padua nucleic acids for use in gene therapy and FIX-Padua polypeptides for use in FIX replacement therapy.

On June 13, 2018, we were granted European Patent 2337849 directed to a FIX polypeptide protein. The opposition period with respect to such patent expired on March 13, 2019, by which time five parties had filed an opposition. On July 25, 2019, we submitted responses to such oppositions with the European Patent Office ("EPO"). Oral proceedings were scheduled for June and July 2020 but were postponed due to COVID-19. New dates for virtual oral proceedings have been set for May 2021. In addition, on May 15, 2019, a divisional European patent application in the FIX-Padua family, EP 3252157, was refused. In September 2019, we filed a notice of appeal with respect to such refusal. We are also pursuing a European divisional patent application that was filed on May 14, 2019. Both in the U.S. and in Europe, we have pending divisional applications still in prosecution phases. The appeal process has been delayed as a result of the COVID-19 pandemic, and we do not currently know when the appeal is likely to be resolved.

On January 4, 2020, a petition seeking Inter Partes Review of U.S. Patent No. 9,249,405 (the "'405 Patent") was filed by Pfizer, Inc. (the "IPR Proceeding"). The petition sought to invalidate claims 6 and 9-15 of the '405 Patent. On April 17, 2020, we filed our preliminary response to the petition, disclaiming claims 6 and 9-13 of the '405 patent and otherwise requesting the denial of the petition. On July 13, 2020, the United States Patent and Trademark Office issued its decision to institute the Inter Partes Review. On October 13, 2020, we filed a motion to amend the patent claims at issue in the proceeding. On January 13, 2021, Pfizer filed a brief in opposition to our motion to amend the claims. On February 3, 2021 the Patent Appeals Board of the USPTO (the "PTAB") provided its preliminary guidance with respect to the proposed amended claims, which stated among other things that the proposed amended claims were not anticipated but were obvious in light of the cited prior art. On February 16, 2021 and in response to the preliminary guidance, we moved to dismiss our motion to amend the claims before the PTAB and requested an adverse judgement in the IPR Proceeding. As a result, we expect to maintain the currently issued and unchallenged claims of the '405 Patent and pursue additional claims based on our proposed amended claims in continuation applications before the USPTO.

Phase I/II Clinical Trial of AMT-060

In the third quarter of 2015, we initiated a Phase I/II clinical trial of AMT-060, our first-generation hemophilia B product candidate, in patients with severe or moderately-severe hemophilia B. AMT-060 consists of an AAV5 vector carrying a codon-optimized, wild-type, human FIX gene cassette licensed from St. Jude Children's Research Hospital. The study is a five-year, open-label, uncontrolled, single-dose, dose-ascending multi-center trial that includes two cohorts, with the low-dose cohort using a treatment of $5x10^{12}$ gc/kg and the second-dose cohort using $2x10^{13}$ gc/kg. We enrolled five patients into the low dose cohort in the third quarter of 2015. Another five patients were enrolled into the high dose cohort between March and May 2016.

In December 2020, we presented five-year follow-up data related to this Phase I/II clinical trial. All 10 patients enrolled continue to show long-term clinical benefit, including sustained increases in FIX activity, reduced usage of FIX replacement therapy, and decreased bleeding frequency. At up to five years of follow-up, AMT-060 continues to be well-tolerated, with no new treatment-related adverse events since the last reported data and no development of inhibitors during the study.

All five patients in the second dose cohort of $2x10^{13}$ gc/kg (the same dose being studied in the Phase III HOPE-B study of etranacogene dezaparvovec) continue to be free of routine FIX replacement therapy at four-and-a-half years after treatment. Based on the six months of data collected during the fifth year of follow-up, the mean annualized bleeding rate was zero compared to an average of four bleeds during the year prior to treatment, representing a 100% reduction. During this same period, the usage of FIX replacement therapy declined to zero compared to 354,800 IU in the year prior to treatment, representing a 100% reduction. Mean FIX activity over 4.5 years was 7.4% (compared to 7.5% at three and a half years, 7.9% in the third year, 8.4% in the second year and 7.1% in the first year), while in the lower dose cohort, mean FIX activity was 5.2% over 5 years since treatment.

Fabry disease program (AMT-190)

Fabry Disease and Market Background

Fabry disease is a progressive, inherited, multisystemic lysosomal storage disease characterized by specific neurological, cutaneous, renal, cardiovascular, cochleo-vestibular, and cerebrovascular manifestations. Fabry disease is caused by a defect in a gene that encodes for a protein called α-galactosidase A ("GLA"). The GLA protein is an essential enzyme required to breakdown globotriaosylsphingosine ("Gb3") and lyso-globotriaosylsphingosine ("lyso-Gb3"). In patients living with Fabry disease, Gb3 and lyso-Gb3 accumulate in various cells throughout the body causing progressive clinical signs and symptoms of the disease. Current treatment options, which consist of bi-weekly intravenous enzyme replacement therapy, typically have no therapeutic benefit in patients with advanced renal or cardiac disease. Studies have also shown that a majority of male patients develop antibodies that inhibit the GLA protein and interfere with therapeutic efficacy.

Fabry disease has two major disease phenotypes: the type 1 "classic" and type 2 "later-onset" subtypes. Both lead to renal failure, and/or cardiac disease, and early death. Type 1 males have little or no functional a-Gal A enzymatic activity (<1% of normal mean) and marked accumulation of GL-3/Gb3 and related glycolipids in capillaries and small blood vessels which cause the major symptoms in childhood or adolescence. In contrast, males with the type 2 "later-onset" phenotype (previously called cardiac or renal variants) have residual a-Gal A activity, lack GL-3/Gb3 accumulation in capillaries and small blood vessels, and do not manifest the early manifestations of type 1 males. They experience an essentially normal childhood and adolescence. They typically present with renal and/or cardiac disease in the third to seventh decades of life. Most type 2 later-onset patients have been identified by enzyme screening of patients in cardiac, hemodialysis, renal transplant, and stroke clinics and recently by newborn screening. Fabry disease occurs in all racial and ethnic populations and affects males and females. It is estimated that type 1 classic Fabry disease affects approximately one in 40,000 males. The type 2 later-onset phenotype is more frequent, and in some populations may occur as frequently as about 1 in 1,500 to 4,000 males.

Our Development of AMT-190 for Fabry Disease

In September 2020, we selected a lead gene therapy candidate (AMT-190) for the treatment of Fabry disease to advance into IND-enabling studies. The lead candidate is a one-time administered AAV5 gene therapy incorporating the GLA transgene. In preclinical studies comparing multiple product candidates, including constructs incorporating a modified alpha-N-acetylgalactosaminidase transgene (modNAGA), AMT-190 demonstrated the most robust and sustained increases in GLA activity.

Hemophilia A program (AMT-180)

In June 2020, we announced that we plan to de-prioritize our research program of AMT-180 for patients with hemophilia A, as part of our effort to focus on those gene therapy programs that have the greatest potential to improve patients' lives and generate long-term value for shareholders.

Central Nervous System diseases

Huntington's Disease

Huntington's Disease and Market Background

Huntington's disease is a severe genetic neurodegenerative disorder causing loss of muscle coordination, behavioral abnormalities, and cognitive decline, often resulting in complete physical and mental deterioration over a 12 to 15-year period. The median survival time after onset is 15 to 18 years (range: 5 to >25 years). Huntington's disease is caused by an inherited defect in a single gene that codes for a protein called Huntingtin ("HTT"). The prevalence of Huntington's disease is three to seven per 100,000 in the general population, similar in men and women, and it is therefore considered a rare disease. Despite the ability to identify Huntington's disease mutation carriers decades before onset, there is currently no available therapy that can delay onset or slow progression of the disease. Although some symptomatic treatments are available, they only are transiently effective despite significant side effects.

Our Development of AMT-130 for Huntington's Disease

AMT-130 is our gene therapy candidate targeting Huntington's disease that utilizes an AAV vector carrying an engineered micro ribonucleic acid ("miRNA") designed to silence HTT and exon 1 HTT, a potentially highly toxic protein fragment that may also contribute to disease pathology. AMT-130 comprises a recombinant AAV5 vector carrying a deoxyribonucleic acid ("DNA") cassette, encoding a miRNA that non-selectively lowers or knocks-down HTT and exon 1 HTT in Huntington's disease patients. AMT-130 was developed using our miQURE technology, a proprietary, one-time administered gene silencing platform. AMT-130 has received orphan drug designation from the FDA and Orphan Medicinal Product Designation from the EMA. AMT-130 is intended to be administered directly into the brain via a stereotactic, magnetic resonance imaging guided catheter.

Our goal for AMT-130 is to develop a gene therapy with the following profile:

(1) One-time administration of disease-modifying therapy into the striatum, the area of the brain where Huntington's disease is known to manifest;
(2) Biodistribution of the therapy in both the deep and cortical structures of the brain via transport of the AAV vector and through secondary exosome-mediated delivery; and
(3) Safe, on-target and durable knockdown of HTT and exon 1 HTT.

In April 2018, we presented an overview of preclinical data establishing proof-of-concept for AMT-130 at the 2018 American Academy of Neurology Annual Meeting in Los Angeles, California. Data from multiple studies in Huntington's disease animal models across three different species showed that a single intraparenchymal administration of AMT-130 into the striatum, resulted in a dose-dependent and sustained reduction of mutant huntingtin protein ("mHTT") in both the deep structures of the brain and the cortex. Specifically, we presented data from the ongoing preclinical study in transgenic minipigs, one of the largest Huntington's disease animal models available, demonstrating significant reductions in human mHTT by a median of 68% in the striatum and a median of 47% in the frontal cortex at 6 months after administration of AMT-130.

In January 2019, our IND application for AMT-130 was cleared by the FDA and in the fourth quarter of 2019 we initiated patient screening for a Phase I/II study. The Phase I/II protocol is a randomized, imitation surgery-controlled, double-blinded study conducted at three surgical sites, and multiple referring, non-surgical sites in the U.S. The primary objective of the study is to evaluate the safety, tolerability and efficacy of AMT-130 at two doses.

In February 2019, we presented new preclinical data at the 14th Annual CHDI Huntington's disease Therapeutics Conference that illustrate the therapeutic potential of AMT-130 in restoring function of damaged brain cells in Huntington's disease. In that study, AMT-130 was generally well-tolerated and resulted in a sustained reduction of mutant huntingtin protein.

In June 2020, we announced the completion of the first two patient procedures in the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease. These procedures occurred after a postponement that resulted from the COVID-19 pandemic and the associated states of emergency declarations in the United States. The Phase I/II protocol is a randomized, imitation surgery-controlled, double-blinded study conducted at three surgical sites, and multiple referring, non-surgical sites in the U.S. The primary objective of the study is to evaluate the safety, tolerability, and efficacy of AMT-130 at two doses.

On September 25, 2020, we announced that the independent DSMB overseeing the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease had met and reviewed 90-day safety data from the first two patients enrolled in the trial. No significant safety concerns were noted to prevent further dosing.

On October 13, 2020, we announced the completion of the third and fourth patient procedures in the Phase I/II clinical trial.

On February 8, 2021, we announced that the DSMB had met and reviewed the six-month safety data from the first two enrolled patients and the 90-day safety data from the next two enrolled patients in the study. No significant safety concerns were noted to prevent further dosing, and the final six patients in the first cohort are now cleared for enrollment.

Spinocerebellar Ataxia Type 3 program

Spinocerebellar Ataxia type 3 and Market Background

Spinocerebellar Ataxia type 3 ("SCA3"), also known as Machado-Joseph disease, is a central nervous system disorder caused by a cytosine-adenine-guanine ("CAG")-repeat expansion in the ATXN3 gene that results in an abnormal form of the protein ataxin-3. Patients with SCA3 experience brain degeneration that results in movement disorders, rigidity, muscular atrophy, and paralysis. There is currently no treatment available that slows the progressive course of this potentially lethal disease.

Prevalence of SCA3 is estimated to be one to two per 100,000 with significant geographical and ethnic variations, with the highest prevalence rates observed in the Azores (Flores Island (1/239)), the intermediate prevalence rates observed in Portugal, Germany, the Netherlands, China and Japan, and the lower prevalence observed in North America, Australia, and India. SCA3 is the most common form of autosomal dominant cerebellar ataxia ("ADCA") type 1 in most genetically characterized populations.

Our preclinical SCA3 program (AMT-150)

AMT-150 is a one-time, intrathecally-administered, AAV gene therapy incorporating our proprietary miQURE silencing technology that is designed to halt ataxia in early manifest SCA3 patients. In an in-vitro study with human induced pluripotent stem ("IPS") derived neurons, AMT-150 has been shown to lower the human ataxin-3 protein by 65%, without any off-target effects. We also performed a proof-of-concept in-life study in SCA3 mice demonstrating that AMT-150 was able to lower toxic ataxin-3 protein by up to 53% in the cerebellum and up to 65% in the brain stem after a single administration. Further studies in non-human primates ("NHP") demonstrate the ability to distribute and express a reporter gene in the most degenerated brain regions in SCA3. In these preclinical studies, a single administration of AMT-150 resulted in sustained expression and efficient processing with on-target engagement. Additionally, AMT-150 lacked off-target activity in these studies.

At the 2019 American Academy of Neurology Annual Meeting, we presented preclinical data on AMT-150 demonstrating mechanistic proof-of-concept of the non-allele-specific ataxin-3 protein-silencing approach by using artificial miRNA candidates engineered to target the ataxin-3 gene in a SCA3 knock-in mouse model. In this proof-of-concept study, a single AMT-150 injection in the cerebrospinal fluid resulted in AAV transduction and mutant ataxin-3 lowering at the primary sites of disease neuropathology, the cerebellum (up to 53%) and the brainstem (up to 65%).

In May 2020, we presented preclinical data at the American Society of Gene and Cell Therapy ("ASGCT") Annual Meeting, on our gene therapy candidate SCA3. In an in vivo preclinical study, six NHP received a one-time injection of AMT-150 via the cisterna magna to assess expression and distribution. Samples taken after eight weeks showed widespread transduction of the brain and spinal cord, with the highest genome copies found in the posterior fossa and cortical regions. In other preclinical studies, researchers evaluated AMT-150 in SCA3 mouse models, as well as human induced pluripotent stem cell ("iPSC")-derived neurons and astrocytes, to investigate potential off-target effects of AAV5-micro ataxin type 3 ("miATXN3"). The iPSC-derived cell cultures, which were derived from two SCA3 patients, represent the most disease-relevant cell type for therapeutic targeting of AMT-150. A clear dose-dependent expression of miATXN3 was observed in the iPSC-derived neurons and astrocytes transduced with AMT-150. Mature miATXN3 molecules were also associated with extracellular vesicles that strongly correlated with the dose and miATXN3 expression, suggesting the potential therapeutic spread of the engineered miATXN3. Additionally, AMT-150 demonstrated ATXN3 knockdown in human neurons and various SCA3 mouse models with subsequent neuropathology improvement.

In September 2020, we initiated a safety and toxicology study of AMT-150 in NHP.

New Technology Development

We are seeking to develop next-generation technologies with the goal of further improving the potential of AAV-based gene therapies to treat patients suffering from debilitating diseases.

We are focused on innovative technologies across each of the key components of an AAV-based gene therapy, including: (i) the capsid, or the outer viral protein shell that encloses the target DNA; (ii) the promoter, or the DNA sequence that drives the expression of the transgene; and (iii) the transgene, or therapeutic gene.

We dedicate significant effort to designing and screening novel AAV capsids with the potential for (i) higher biological potency; (ii) increased specificity and penetration of specific tissue types; and (iii) enhanced safety. We believe we have significant expertise in vector engineering and have created promising genetically engineered capsids using a "rational design" approach.

In addition to the directed evolution approach where we screen a library of AAV mutants, we are also rationally engineering the AAV capsids to target them to specific cells and/or tissues. Using such engineered AAV capsids will ensure selected transduction of the targeted, desired cell type. The strategy will diminish potential off target effects.

We work extensively on designing synthetic promoters with the potential of enabling higher levels of protein expression in specific tissue types. A "promoter" is an essential component of a gene therapy construct that controls expression of a therapeutic protein. Synthetic promoters, which do not exist in nature, are optimally tailored to drive gene expression at a desired level and specificity.

To further tailor gene therapies to optimally address certain disorders we may also incorporate specific modifications into the transgenes of our gene therapy constructs. For example, we incorporated the Padua-FIX variant into our hemophilia B gene therapy to substantially increase the resulting FIX activity and potentially improve clinical outcomes. For other programs, such as our gene therapy construct for Fabry disease, we have also utilized modified transgenes with the goal of enhancing efficacy, durability, and safety, as well as expanding the access of gene therapies to patients with inhibitors.

We have also demonstrated the ability to deliver engineered DNA constructs that can silence or suppress disease-causing genes. Our miQURE gene silencing platform, based on exclusively licensed technology from Cold Spring Harbor Laboratory ("CSHL"), is designed to degrade mutated genes without off-target toxicity and induce silencing of the mutated gene in the entire target organ through secondary exosome-mediated delivery. miQURE-based gene therapy candidates, such as AMT-130, incorporate proprietary, therapeutic miRNA constructs that can be delivered using AAVs to potentially provide long-lasting activity. Preclinical studies of miQURE-based gene therapies have demonstrated several important advantages, including enhanced tissue-specificity, improved nuclear and cytoplasmic gene lowering and no off-target effects associated with impact to the cellular miRNA or messenger RNA transcriptome.

Commercial-Scale Manufacturing Capabilities

The ability to reliably produce at a high quality and at commercial scale is a critical success factor in AAV gene therapy. We produce our gene therapies at our state-of-the-art, Lexington, Massachusetts-based manufacturing facility using a proprietary baculovirus expression vector system.

We believe our integrated manufacturing capabilities provide us several potential advantages, including:

(1) *Know-how.* Since our founding in 1998, we have invested heavily in developing optimized processes and methods to reliably and reproducibly manufacture AAV-based gene therapies at commercial scale. During this time, we have accumulated significant internal experience and knowledge of the underlying production technology and critical quality attributes of our products. These learnings have been essential in developing a modular, third generation production system that can be used to produce all our gene therapy products.

(2) *Flexibility.* Controlling cGMP manufacturing allows us to rapidly adapt our production schedule to meet the needs of our business. By controlling our manufacturing, we do not rely on contract manufacturers, nor do we require costly and time-consuming technology transfers to third parties. Our facility is designed to commercially supply multiple products and are flexibly designed to accommodate expansion and scale up as our needs change.

(3) *Faster Path to Market.* We believe our manufacturing platform enables us to rapidly produce new products for clinical investigation, minimize time between clinical phases and complete scale-up as product candidates advance into late-stage development and commercialization. For example, in transitioning our hemophilia B program from AMT-060 to AMT-061, we were able to rapidly demonstrate manufacturing comparability and produce clinical material for our ongoing Phase III pivotal study, thereby accelerating our time to market.

(4) *High Purity.* The baculovirus system eliminates the risk of introducing mammalian cell derived impurities.

(5) *Scalability.* We have demonstrated our manufacturing process is reproducible at volumes ranging from 2 liters to 500 liters and believe it is possible to achieve higher scale production with our insect-cell, baculovirus system.

(6) *Low Cost of Goods.* We believe our ability to scale production has the potential to significantly reduce unit costs. Our manufacturing process also utilizes fully disposable components, which enables faster change-over times between batches and lower costs associated with cleaning and sterilization. Additionally, our production system does not require the use of plasmids, which can be a costly raw material.

Intellectual Property

Introduction

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection in the United States, Europe, and other countries for novel components of gene therapies, the chemistries, and processes for manufacturing these gene therapies, the use of these components in gene therapies, our technology platform, and other inventions and related technology. We also rely on trade secrets, security measures and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We expect that our probability of success will be significantly enhanced by our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of AAV-based gene therapies.

In some cases, we are dependent on the patented or proprietary technology of third parties to develop and commercialize our products. We must obtain licenses from such third parties on commercially reasonable terms, or our business could be harmed, possibly materially. For example, we license from third parties essential parts of the therapeutic gene cassettes as well as the principal AAV vectors we use and key elements of our manufacturing process. We anticipate that we will require additional licenses in the future.

Because most patent applications throughout the world are confidential for 18 months after the earliest claimed priority date, and since the publication of discoveries in the scientific and patent literature often lags actual discoveries, we cannot be certain that we were the first to invent or file applications for the inventions covered by our pending patent applications. Moreover, we may have to participate in post-grant proceedings in the patent offices of the United States or foreign jurisdictions, such as oppositions, reexaminations, or interferences, in which the patentability or priority of our inventions are challenged. Such proceedings could result in substantial cost, even if the eventual outcome is favorable to us.

Our intellectual property portfolio consists of owned and in-licensed patents, copyrights, licenses, trademarks, trade secrets and other intellectual property rights.

Patent Portfolio

Our gene therapy programs are protected by patents and patent applications directed to various aspects of our technology. For example, our gene therapy programs are protected by patents and patent applications with composition-of-matter or method of use claims that cover the therapeutic gene, the promoter, the viral vector capsid, or other specific parts of these technologies. We also seek protection of core aspects of our manufacturing process, particularly regarding our baculovirus expression system for AAV vectors in insect cells. In addition, we have filed manufacturing patent applications with claims directed to alternative compositions-of-matter and manufacturing processes to seek better protection from competitors.

We file the initial patent applications for our commercially important technologies in both Europe and the United States. For the same technologies, we typically file international patent applications under the PCT within a year. We also may seek, usually on a case-by-case basis, local patent protection in Canada, Australia, Japan, China, India, Israel, South Africa, New Zealand, South Korea, and Eurasia, as well as South American jurisdictions such as Brazil and Mexico.

As of December 31, 2020, our intellectual property portfolio included 99 issued or granted patents and 121 pending patent applications. The geographic breakdown of our owned and exclusively in-licensed patent portfolio was as follows:

- 26 issued U.S. patents;
- 13 granted European patents;
- 7 pending PCT patent applications;
- 18 pending U.S. patent applications;
- 20 pending European patent applications; and
- 83 pending and 60 granted patent applications in other jurisdictions.

These patents relate to a variety of technologies including our product candidates that are in development and our manufacturing and technology platform.

Our Patent Portfolio Related to Certain Development Programs

Hemophilia B (AMT-061)

We own a patent family, including patents and patent applications, directed to the use of the Padua mutation in hFIX for gene therapy in etranacogene dezaparvovec. A PCT application was filed on September 15, 2009, and patents have been issued in the United States, Europe, and Canada. Further applications are pending in the United States (three issued patents), Europe, and Hong Kong. The issued patents include claims directed to FIX protein with a leucine at the R338 position of the protein sequence, nucleic acid sequences coding for this protein, and therapeutic applications, including gene therapy. The standard 20-year patent term of patents in this family will expire in 2029.

On June 13, 2018, we were granted European Patent 2337849 directed to a polypeptide protein. The opposition period with respect to such patent expired on March 13, 2019, by which time five parties had filed an opposition. On July 25, 2019, we submitted responses to such oppositions with the EPO and oral proceedings with respect to such oppositions were scheduled for June and July 2020 but were postponed due to COVID-19. New dates for virtual oral proceedings have been set for May 2021. In addition, on May 15, 2019, a divisional European patent application in the FIX-Padua family, EP 3252157, was refused. In September 2019, we filed a notice of appeal with respect to such refusal. We are also pursuing a European divisional patent application that was filed on May 14, 2019. Both in the U.S. and in Europe, we have pending divisional applications still in prosecution phases. The appeal process has been delayed as a result of the COVID-19 pandemic, and we do not currently know when the appeal is likely to be resolved.

On November 5, 2019, the USPTO granted us a third patent, U.S. Patent Number 10,465,180, which covers any AAV comprising a nucleic acid encoding a FIX-Padua protein, and promoter sequences, transcription termination and control elements. The claims also cover FIX-Padua variants with at least 70% sequence identity to FIX-R338L.

On January 4, 2020, the IPR Proceeding was filed by Pfizer, Inc. The petition sought to invalidate claims 6 and 9-15 of the ‘405 Patent. On April 17, 2020, we filed our preliminary response to the petition, disclaiming claims 6 and 9-13 of the ‘405 patent and otherwise requesting the denial of the petition. On July 13, 2020, the United States Patent and Trademark Office issued its decision to institute the Inter Partes Review. On October 13, 2020, we filed a motion to amend the patent claims at issue in the proceeding. On January 13, 2021, Pfizer filed its opposition to our motion to amend the claims. On February 3, 2021 the PTAB provided its preliminary guidance with respect to the proposed amended claims, which stated among other things that the proposed amended claims were not anticipated but were obvious in light of the cited prior art. On February 16, 2021 and in response to the preliminary guidance, we moved to dismiss our motion to amend the claims before the PTAB and requested an adverse judgement in the IPR Proceeding. As a result, we expect to maintain the currently issued and unchallenged claims of the ‘405 Patent and pursue additional claims based on our proposed amended claims in continuation applications before the USPTO.

Huntington’s disease (AMT-130)

We own a patent family directed to gene therapy treatment of Huntington’s disease within AMT-130. This family includes an issued patent in the United States and pending patent applications in the US, Europe, and other jurisdictions. The standard 20-year term of patents in this family will expire in 2035.

In May 2019, we announced the issuance of two new patents covering AMT-130, U.S. Patent 10,174,321 and European Patent EP 3237618 B1. The claims as granted cover the RNA constructs specifically designed to target exon1 and the embedding of these Huntington’s disease RNA sequences into the miR451 scaffold, which is exclusively licensed to us from CSHL. The claims also cover certain expression cassettes comprising the RNA constructs and the use of gene therapy vectors including AAV vectors encompassing the described expression cassettes. In addition, this patent family has multiple pending family members, including pending applications in U.S. and Europe.

AMT-130 incorporates our proprietary miQURE gene silencing technology platform, which is designed to degrade disease-causing genes, without off-target toxicity, and induce silencing of the entire target organ through secondary exosome-mediated delivery. We have filed additional patent applications related to this technology generally and AMT-130, specifically which will potentially provide further patent protection for our Huntington’s disease clinical candidate AMT-130.

Licenses

We have obtained exclusive or non-exclusive rights from third parties under a range of patents and other technology that we use in our product and development programs, as described below. Our agreements with these third parties generally grant us a license to make, use, sell, offer to sell, and import products covered by the licensed patent rights in exchange for our payment of some combination of an upfront amount, annual fees, royalties, a percentage of amounts we receive from our licensees and payments upon the achievement of specified development, regulatory or commercial milestones. Some of the agreements specify the extent of the efforts we must use to develop and commercialize licensed products. The agreements generally expire upon expiration of the last-to-expire valid claim of the licensed patents. Each licensor may terminate the applicable agreement if we materially breach our obligations and fail to cure the breach within a specified cure period.

Technology Used for Multiple Programs

We are exploiting technology from third-party sources described below in more than one of our programs.

Cold Spring Harbor Laboratory

In 2015, we entered into a license agreement with CSHL in which CSHL granted to us an exclusive, sublicensable license to develop and commercialize certain of CSHL's patented RNAi-related technology for use in connection with the treatment or prevention of Huntington's disease. The standard 20-year patent term for the licensed patents expires in 2031.

In 2018, we entered into an amendment of the license agreement with CSHL that expanded the license to include the diagnosis, treatment, or prevention of all CNS diseases in the Field, including but not limited to Huntington's disease. In addition, under the amended license agreement CSHL granted to us an exclusive license for a three-year term to develop and commercialize therapeutic products for the additional disease classifications in the Field of liver diseases, neuromuscular diseases, and cardiovascular diseases. If we meet certain diligence milestones during the initial three-year development term, we may include exclusively additional disease classifications within the additional Fields on similar terms and conditions as the CNS diseases. We are currently using the technology in our Huntington's disease and SCA 3 programs.

Under this license agreement, annual fees, development milestone payments and future single-digit royalties on net sales of a licensed product are payable to CSHL.

Protein Sciences

In 2016, we revised our existing license contract with Protein Sciences Corporation for the use of its *expresSF+* insect cell line and associated technology for human therapeutic and prophylactic uses (except influenza) to provide us with a royalty free, perpetual right and license to the licensed technology in the field of AAV-based gene therapy.

Technology Used for Specific Development Programs

Hemophilia B

National Institutes of Health—AAV production

In 2007, we entered into a non-exclusive license agreement with the NIH, which we amended in 2009 and 2013. The patents under this license cover technology to produce AAV vectors in insect cells. We may only grant sublicenses under this agreement with the NIH's consent, which may not be unreasonably withheld. The standard 20-year term for the underlying patents will expire in 2022.

Payment obligations to the NIH under this license agreement include a low single-digit percentage royalty on the net sales of licensed products by us or on our behalf; development and regulatory milestone payments; and an annual maintenance fee creditable against royalties. We do not have to pay royalties or milestone fees under this agreement if we must pay royalties or milestone fees under our 2011 agreement with the NIH, described below, for the same product. Under the license agreement, we have agreed to meet benchmarks in our development efforts, including as to development events, clinical trials, and marketing approval, within specified timeframes.

The NIH may terminate this agreement in specified circumstances relating to our insolvency or bankruptcy. We may terminate this agreement for any reason, in any territory, subject to a specified notice period.

National Institutes of Health—AAV5

In 2011, we entered into another license agreement with the NIH, superseding an earlier agreement. This agreement was amended in 2016. Under this agreement, the NIH granted us an exclusive, worldwide license to patents relating to AAV5 for use in therapeutic products to be delivered to the brain or liver for treatment of human diseases originating in the brain or liver but excluding arthritis-related diseases, and a non-exclusive, worldwide license to patents relating to AAV5 for all other diseases. The license technology under the patents of this license is also used in connection with the Huntington's disease program. We refer to the products licensed under this agreement as AAV5 products. We may grant sublicenses under this agreement only with the NIH's consent, which may not be unreasonably withheld. The standard 20-year term for the underlying patents expired in 2019, but there are U.S. patents still in force of which the latest will expire in 2021.

Payment obligations to the NIH under this license agreement include royalties equal to a low single-digit percentage of net sales of AAV5 products; development and regulatory milestone payments; and an annual maintenance fee creditable against royalties. If an AAV5 product is also covered by our 2007 agreement with the NIH, our obligation to pay royalties on net sales and our obligation to pay milestone fees only apply under this 2011 agreement and not the 2007 agreement. We have agreed to meet benchmarks in our development efforts, including as to development events, clinical trials, and marketing approval, within specified timeframes.

The NIH may terminate this agreement in specified circumstances relating to our insolvency or bankruptcy. We may terminate this agreement for any reason, in any country or territory, subject to a specified notice period.

Padua

On April 17, 2017, we entered into an Assignment and License Agreement with Dr. Simioni (the "Padua Assignment"). Pursuant to the Padua Assignment, we acquired from Dr. Simioni all right, title and interest in a patent family covering the variant of the FIX gene, carrying an R338L mutation (FIX-Padua; "Padua IP"). Under the Padua Assignment, we have also licensed certain know-how included in the Padua IP. We will provide Dr. Simioni with an initial license fee and reimbursement of past expenses, as well as payments that may come due upon the achievement of certain milestone events related to the development of the Padua IP and may also include royalties on a percentage of certain revenues. We have granted a license of the Padua IP back to Dr. Simioni for therapeutic or diagnostic use of a modified Factor IX protein (other than in connection with gene therapy) and any application for non-commercial research purposes. We have agreed to indemnify Dr. Simioni for claims arising from our research, development, manufacture, or commercialization of any product making use of the Padua IP, subject to certain conditions. The Padua Assignment will remain in effect, unless otherwise terminated pursuant to the terms of the Padua Assignment, until the later of (i) the expiration date of the last of the patents within the Padua IP and (ii) the expiration of the payment obligations under the Padua Assignment.

St. Jude Children's Research Hospital

In 2008, we entered into a license agreement with St. Jude, which we amended in 2012. Under this license agreement, St. Jude has granted us an exclusive license, with a right to sublicense, to patent rights relating to expression of hFIX in gene therapy vectors, to make, import, distribute, use, and commercialize products containing hFIX covered by a valid patent claim in the field of gene therapy for treatment or prophylaxis of hemophilia B. In addition, we have a first right of negotiation regarding any patent applications that are filed by St. Jude for any improvements to the patent rights licensed to us. The U.S. patent rights will expire in 2028 and the European patents will expire in 2025.

We have agreed to pay St. Jude a royalty equal to a low single-digit percentage of net sales, if any, by us or our sublicensees of products covered by the licensed patent rights, and a portion of certain amounts we receive from sublicensees ranging from a mid-single digit to a mid-teen double-digit percentage of such amounts. We have also agreed to pay St. Jude one-time milestone fees totaling $6.5 million upon the achievement of specified development and regulatory milestones, and an annual maintenance fee creditable against royalties and milestones in the same year. We have agreed to use commercially reasonable efforts to diligently develop and commercialize products licensed under this agreement.

The agreement will remain in effect until no further payment is due relating to any licensed product under this agreement or either we or St. Jude exercise our rights to terminate it. St. Jude may terminate the agreement in specified circumstances relating to our insolvency. We may terminate the agreement for convenience at any time subject to a specified notice period.

Trade Secrets

In addition to patents and licenses, we rely on trade secrets and know-how to develop and maintain our competitive position. For example, significant aspects of the process by which we manufacture our gene therapies are based on unpatented trade secrets and know-how. We seek to protect our proprietary technology and processes and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial collaborator. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Trademarks

We have a number of material registered trademarks, including "uniQure", that we have registered in various jurisdictions including the United States and the European Union. We may seek trademark protection for other product candidates and technologies as and when appropriate.

Competition

The biotechnology and pharmaceutical industries, including in the gene therapy field, are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions and governmental agencies and public and private research institutions.

We are aware of numerous companies focused on developing gene therapies in various indications, including Applied Genetic Technologies Corp., Abbvie, Abeona Therapeutics, Adverum Biotechnologies, Ally Therapeutics, Apic Bio, Asklepios BioPharmaceutical, Astellas, AVROBIO, Bayer, Biogen, BioMarin, bluebird bio, CRISPR Therapeutics, Editas Medicine, Expression Therapeutics, Fate, Freeline Therapeutics, Generation Bio, Genethon, GlaxoSmithKline, Homology Medicines, Intellia Therapeutics, Johnson & Johnson, Krystal Biotech, Lexeo Therapeutics, LogicBio Therapeutics, Lysogene, MeiraGTx, Milo Biotechnology, Mustang Bio, Novartis, Orchard Therapeutics, Oxford Biomedica, Passage Bio, Pfizer, REGENXBIO, Renova Therapeutics, Roche, Rocket Pharmaceuticals, Sangamo Therapeutics, Sanofi, Selecta Biosciences, Sarepta Therapeutics, Sio Therapeutics, Solid Biosciences, SwanBio, Takeda, Taysha Gene Therapies, Ultragenyx, Vivet Therapeutics, and Voyager Therapeutics, as well as several companies addressing other methods for modifying genes and regulating gene expression. We may also face competition with respect to the treatment of some of the diseases that we are seeking to target with our gene therapies from protein, nucleic acid, antisense, RNAi and other pharmaceuticals under development or commercialized at pharmaceutical and biotechnology companies such as Alnylam Pharmaceuticals, Bayer, BioMarin, CSL Behring, Dicerna Pharmaceuticals, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Pfizer, Translate Bio, Roche, Sanofi, Sobi, Takeda, WaVe Life Sciences, and numerous other pharmaceutical and biotechnology firms.

We also compete with existing standards of care, therapies, and symptomatic treatments, as well as any new therapies that may become available in the future for the indications we are targeting.

Many of our current or potential competitors, either alone or with their collaborators, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all our programs are likely to be their efficacy, safety, convenience, price, and the availability of reimbursement from government and other third-party payers. We also believe that, due to the small size of the patient populations in the orphan indications we target, being first to market will be a significant competitive advantage. We believe that our advantages in vector and manufacturing technology will allow us to reach market in a number of indications ahead of our competitors, and to capture the markets in these indications.

Government Regulation and Reimbursement

Government authorities in the United States, European Union and other countries extensively regulate, among other things, the approval, research, development, preclinical and clinical testing, manufacture (including any manufacturing changes), packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, reimbursement, and import and export of pharmaceutical products, biological products, and medical devices. We believe that all our product candidates will be regulated as biological products, or biologics, and in particular, as gene therapies, and will be subject to such requirements and regulations under U.S. and foreign laws. For other countries outside of the United States and the European Union, marketing approval and pricing and reimbursement requirements vary from country to country. If we fail to comply with applicable regulatory requirements, we may be subject to, among other things, fines, refusal to approve pending applications, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions, and criminal prosecution.

Regulation in the United States

In the United States, the FDA regulates biologics under the Public Health Service Act ("PHSA") and the Federal Food, Drug, and Cosmetic Act ("FDCA") and regulations and guidance implementing these laws. These laws and regulatory guidance are continually evolving. By example, in March 2020, the U.S. Congress passed the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, which includes various provisions regarding FDA drug shortage reporting requirements, as well as provisions regarding supply chain security, such as risk management plan requirements, and the promotion of supply chain redundancy and domestic manufacturing. The FDA has also issued a number of guidance documents concerning how sponsors and investigators may address COVID-19 challenges, including challenges specific to gene therapies. These guidance documents are continually evolving.

Obtaining regulatory approvals and ensuring compliance with applicable statutes and regulatory requirements entails the expenditure of substantial time and financial resources, including payment of user fees for applications to the FDA. All our current product candidates are subject to regulation by the FDA as biologics. An applicant seeking approval to market and distribute a new biologic in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's current Good Laboratory Practice regulations;
- submission to the FDA of an IND application which allows human clinical trials to begin unless the FDA objects within 30 days; the sponsor of an IND or its legal representative must be based in the United States
- approval by an independent institutional review board ("IRB") and Institutional Biosafety Committee ("IBC") before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with the FDA's current good clinical practices ("cGCP") to establish substantial evidence of the proposed biological product for each indication;
- preparation and submission to the FDA of a Biologics License Application ("BLA");
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods, and controls are adequate to preserve the product's identity, strength, quality, and purity, as well as selected clinical trial sites and investigators to determine cGCP compliance;
- approval of the BLA by the FDA, in consultation with an FDA advisory committee, if deemed appropriate by the FDA; and
- compliance with any post-approval commitments, including Risk Evaluation and Mitigation Strategies ("REMS"), and post-approval studies required by the FDA.

Human Clinical Studies in the United States under an IND

Before initiating clinical studies in the United States or under an IND, investigational product sponsors must first complete pre-clinical studies. Preclinical studies include laboratory evaluation of chemistry, pharmacology, toxicity, and product formulation, as well as animal studies to assess potential safety and efficacy. Such studies must generally be conducted in accordance with the FDA's Good Laboratory Practices ("GLPs").

Clinical trials involve the administration of the investigational biologic to human subjects under the supervision of qualified investigators in accordance with current GCP requirements, which includes requirements for informed consent, study conduct, and IRB review and approval. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of an IND. INDs include preclinical study reports, together with manufacturing information, analytical data, any available clinical data, or literature, and proposed clinical study protocols among other things. A clinical trial may not proceed in the United States unless and until an IND becomes effective, which is 30 days after its receipt by the FDA. The FDA may raise concerns or questions related to one or more components of an IND and place the IND on clinical hold if during its review the FDA determines that study subjects would be exposed to significant risk of illness or injury the trial may be put on clinical hold. 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 trials due to safety concerns or non-compliance.

The protocol and informed consent documents, as well as other subject communications must also be approved by an IRB that continues to oversee that trial. In the case of gene therapy studies, an IBC at the local level must also review and maintain oversight over the particular study, in addition to the IRB. The FDA, an IRB, and IBC, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk or that research requirements are not being met. Information about certain clinical trials, including results, must be submitted within specific timeframes for listing on the ClinicalTrials.gov website. Sponsors or distributors of investigational products for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions must also have a publicly available policy on evaluating and responding to requests for expanded access requests. Investigators must also provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA.

Subsequent clinical protocols and amendments must also be submitted to an active IND but are not subject to the 30-day review period imposed on an original IND. Progress reports detailing the results of the clinical trials must also be submitted at least annually to the FDA and the IRB and more frequently if serious adverse events or other significant safety information is found. There is a risk that once a new protocol or amendment is submitted to an active IND there may be an extended period before the FDA may comment or provide feedback. This may result in a need to modify an ongoing clinical trial to incorporate this feedback or even a clinical hold of the trial. There is also risk that FDA may not provide comments or feedback but may ultimately disagree with the design of the study once a BLA is submitted.

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

- Phase I: The biological product is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early understanding of its effectiveness.
- Phase II: The biological product is administered to a limited patient population to further 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.
- Phase III: The biological product is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the potency and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labelling of the product. Typically, two Phase 3 trials are required by the FDA for product approval. Under some limited circumstances, however, the FDA may approve a BLA based upon a single Phase 3 clinical study plus confirmatory evidence or a single large multicenter trial without confirmatory evidence.

In addition, under the Pediatric Research Equity Act, or PREA, a BLA or BLA supplement for a new active ingredient, indication, dosage form, dosage regimen, or route of administration, must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Orphan products are also exempt from the PREA requirements.

The manufacture of investigational drugs and biologics for the conduct of human clinical trials is subject to cGMP requirements. Investigational drugs and biologics and active ingredients and therapeutic substances imported into the United States are also subject to regulation by the FDA. Further, the export of investigational products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

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 candidate as well as 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, manufacturers must develop methods for testing the identity, strength, quality, potency, 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.

FDA Guidance Governing Gene Therapy Products

The FDA has issued various guidance documents regarding gene therapies that outline additional factors that the FDA will consider at each of the above stages of development and which relate to, among other things, the proper preclinical assessment of gene therapies; the chemistry, manufacturing, and control information that should be included in an IND application; the design and analysis of shedding studies for virus or bacteria based gene therapies; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects and patients who have been exposed to gene therapies via long-term follow-up with associated regulatory reporting.

Compliance with cGMP Requirements

Manufacturers of biologics must comply with applicable cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Manufacturers and others involved in the manufacture and distribution of such products must also register their establishments with the FDA and certain state agencies, and provide the FDA a list of products manufactured at the facilities. Recently, the information that must be submitted to the FDA regarding manufactured products was expanded through the Coronavirus Aid, Relief, and Economic Security, or CARES, Act to include the volume of drugs produced during the prior year. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Discovery of non-compliance may result in the FDA placing restrictions on a product, manufacturer, or holder of an approved BLA, and may extend to requiring withdrawal of the product from the market, among other consequences. 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.

FDA Programs to Expedite Product Development

The FDA has several programs to expedite product development, including fast track designation and breakthrough therapy designation. These are outlined in specific FDA guidance. Under the fast track program, the sponsor of a biologic candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the product candidate. To be eligible for a fast track designation, the FDA must determine that a product candidate is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. This may be demonstrated by clinical or nonclinical data. If granted, the benefits include greater interactions with the FDA and rolling review of sections of the BLA. In some cases, a fast track product may be eligible for accelerated approval or priority review.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, enacted in 2012, a sponsor can request designation of a product candidate as a breakthrough therapy. A breakthrough therapy is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Products designated as breakthrough therapies are eligible for rolling review, intensive guidance on an efficient development program beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, cross disciplinary review.

Biologics studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means the FDA may approve the product 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. A biologic candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, will allow the FDA to withdraw the drug or biologic from the market on an expedited basis. All promotional materials for drug or biologic candidates approved under accelerated regulations are subject to prior review by the FDA.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Submission of a BLA

The results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls, and proposed labeling, among other things, are submitted to the FDA as part of a BLA requesting a license to market the product for one or more indications. The submission of a BLA is subject to an application user fee, products with orphan designation are exempt from the BLA filing fee. The sponsor of an approved BLA is also subject to annual program user fees for each. Orphan products may also be exempt from program fees provided that certain criteria are met. These fees are typically increased annually. Under the Prescription Drug User Fee Act ("PDUFA") the FDA has agreed to specified performance goals in the review of BLAs.

Most such applications are meant to be reviewed within ten months from the filing acceptance date (typically 60 days after date of filing), and most applications for priority review products are meant to be reviewed within six months of the filing acceptance date (typically 60 days after date of filing). Priority review designation may be assigned to product candidates that are intended to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of the serious condition.

The FDA may refuse to file an application and request additional information. In this event, the application must be refiled with the additional information. The refiled application is also subject to assessment of content before the FDA accepts it for review. Once the submission is accepted, the FDA begins an in-depth substantive review. The FDA will assign a date for its final decision for the product (the PDUFA action date) but can extend this date to complete review of a product application. The PDUFA action date is only a goal, thus, the FDA does not always meet its PDUFA dates.

The FDA may also refer certain applications to an advisory committee. Before approving a product candidate for which no active ingredient (including any ester or salt of active ingredients) has previously been approved by the FDA, the FDA must either refer that product candidate to an external advisory committee or provide in an action letter, a summary of the reasons why the FDA did not refer the product candidate to an advisory committee. The FDA may also refer other product candidates to an advisory committee if the FDA believes that the advisory committee's expertise would be beneficial. An advisory committee is typically a panel that includes clinicians and other experts, which review, evaluate, and make a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

The FDA reviews applications to determine, among other things, whether a product candidate meets the agency's approval standards and whether the manufacturing methods and controls are adequate to assure and preserve the product's identity, strength, quality, potency, and purity. Before approving a marketing application, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities, including contract manufacturers and subcontractors, are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a marketing application the FDA will inspect one or more clinical trial sites to assure compliance with GCPs.

After evaluating the marketing application and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the biological product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information for the FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the BLA, the FDA will issue an approval letter. Many drug applications receive complete response letters from the FDA during their first cycle of FDA review.

If the FDA approves a product, it may limit the approved indications for use of the product; require that contraindications, warnings, or precautions be included in the product labeling, including boxed warnings; require that post-approval studies, including Phase IV clinical trials, be conducted to further assess a biologic's efficacy and safety after approval; or require testing and surveillance programs to monitor the product after commercialization. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. The FDA may also not approve label statements that are necessary for successful commercialization and marketing.

In addition to the above conditions of approval, the FDA also may require submission of a REMS to ensure that the benefits of the product candidate outweigh the risks. The REMS plan could include medication guides, physician communication plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. An assessment of the REMS must also be conducted at set intervals. Following product approval, a REMS may also be required by the FDA if new safety information is discovered, and the FDA determines that a REMS is necessary to ensure that the benefits of the product outweigh the risks. In guidance, FDA stated that during the review of a BLA for a gene therapy, it will assess whether a REMS is necessary. Several gene therapy products that have been approved by FDA have required substantial REMS, which included requirements for dispensing hospital and clinic certification, training, adverse event reporting, documentation, and audits and monitoring conducted by the sponsor, among other conditions. REMS, such as these, can be expensive and burdensome to implement, and burdensome for hospitals, clinics, and health care providers to comply with.

Biosimilars and Exclusivity

The Biologics Price Competition and Innovation Act of 2009 ("BPCIA") which amended the PHSA authorized the FDA to approve biosimilars under Section 351(k) of the PHSA. Under the BCPIA, a manufacturer may submit an application for licensure of a biologic product that is biosimilar to or interchangeable with a previously approved biological product or reference product. For the FDA to approve a biosimilar product, it must find that it is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the reference product and proposed biosimilar product in safety, purity or potency. A finding of interchangeability requires that a product is determined to be biosimilar to the reference product, and that the product can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

An application for a biosimilar product may not be submitted to the FDA until four years following approval of the reference product, and it may not be approved until 12 years thereafter. These exclusivity provisions only apply to biosimilar companies and not companies that rely on their own data and file a full BLA. Moreover, this exclusivity is not without limitation. Certain changes and supplements to an approved BLA, and subsequent applications filed by the same sponsor, manufacturer, licensor, predecessor in interest, or other related entity do not qualify for the twelve-year exclusivity period. Further, the twelve-year exclusivity market period in the U.S. for biologics has been controversial and may be shortened in the future.

The PHSA also includes provisions to protect reference products that have patent protection. The biosimilar product sponsor and reference product sponsor may exchange certain patent and product information for the purpose of determining whether there should be a legal patent challenge. Based on the outcome of negotiations surrounding the exchanged information, the reference product sponsor may bring a patent infringement suit and injunction proceedings against the biosimilar product sponsor. The biosimilar applicant may also be able to bring an action for declaratory judgment concerning the patent.

To increase competition in the drug and biologic product marketplace, Congress, the executive branch, and the FDA have taken certain legislative and regulatory steps. By example, in 2020 the FDA finalized a guidance to facilitate biologic product importation. Moreover, the 2020 Further Consolidated Appropriations Act included provisions requiring that sponsors of approved biologic products, including those subject to REMS, provide samples of the approved products to persons developing biosimilar products within specified timeframes, in sufficient quantities, and on commercially reasonable market-based terms. Failure to do so can subject the approved product sponsor to civil actions, penalties, and responsibility for attorney's fees and costs of the civil action. This same bill also includes provisions with respect to shared and separate REMS programs for reference and generic drug products.

Orphan Drug Exclusivity

Under the Orphan Drug Act of 1983, the FDA may designate a biological product as an orphan drug if it is intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a biological product available in the United States for treatment of the disease or condition will be recovered from sales of the product. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan drug designation if there is a product already approved by the FDA that is considered by the FDA to be the same as the already approved product and is intended for the same indication. This hypothesis must be demonstrated to obtain orphan exclusivity. If a product with orphan designation receives the first FDA approval, it will be granted seven years of marketing exclusivity, which means that the FDA may not approve any other applications for the same product for the same indication for seven years, unless clinical superiority is demonstrated. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process. The FDA has granted orphan drug designation to AMT-130 for the treatment of Huntington's disease as well as for etranacogene dezaparvovec; meaning that they would receive orphan drug exclusivity if they are the first products approved for their respective indications. Orphan product sameness decisions are an evolving space when it comes to gene therapies. Specifically, the FDA has issued guidance regarding how it will determine whether a gene therapy product is the same as another product for the purpose of the agency's orphan drug regulations. Any of the FDA sameness determinations could impact our ability to receive approval for our product candidates and to obtain or retain orphan drug exclusivity.

Pediatric Exclusivity

Under the Pediatric Research Equity Act of 2003, pediatric exclusivity provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity in the US, including orphan exclusivity and exclusivity against biosimilars. This six-month exclusivity may be granted if the FDA issues a written request to the sponsor for the pediatric study, the sponsor submits a final study report after receipt of the written request and meets the terms and timelines in the FDA's written request.

Regenerative Advanced Therapy Designation

The 21st Century Cures Act became law in December 2016 and created a new program under Section 3033 in which the FDA has authority to designate a product as a regenerative medicine advanced therapy ("RMAT"). A drug is eligible for a RMAT designation if: 1) it is a regenerative medicine therapy which is a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except those products already regulated under Section 361 of the PHSA; 2) the drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and 3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. A RMAT must be made with the submission of an IND or as an amendment to an existing IND. FDA will determine if a product is eligible for RMAT designation within 60 days of submission. Advantages of the RMAT designation include all the benefits of the fast track and breakthrough therapy designation programs, including early interactions with the FDA. These early interactions may be used to discuss potential surrogate or intermediate endpoints to support accelerated approval. In 2019 the FDA stated in guidance that human gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues, may meet the definition of a regenerative therapy.

FDA Regulation of Companion Diagnostics and Other Combination Products

We may seek to develop companion diagnostics for use in identifying patients that we believe will respond to our gene therapies. Similarly, our product candidates may require delivery devices. A biologic product may be regulated as a combination product if it is intended for use in conjunction with a medical device, such as a drug delivery device or in vitro diagnostic device. For combination products, the biologic and device components must, when used together, be safe and effective and the product labeling must reflect their combined use. In some cases, the medical device component may require a separate premarket submission. Moreover, clinical trial sponsors using investigational devices in their studies must comply with FDA's investigational device exemption regulations. Once approved or cleared, the device component sponsor (or the combination product sponsor, if both components are covered by one application) must comply with the FDA's post-market device requirements, including establishment registration, device listing, device labeling, unique device identifier, quality system regulation, medical device reporting, and reporting of corrections and removals requirements.

If the safety or effectiveness of a biologic product is dependent on the results of a diagnostic, the FDA may require that the in vitro companion diagnostic device and biologic product be contemporaneously approved, with labeling that describes the use of the two products together. The type of premarket submission required for a companion diagnostic device will depend on the FDA device classification. A premarket approval ("PMA"), application is required for high risk devices classified as Class III; a 510(k) premarket notification is required for moderate risk devices classified as Class II; and a de novo request may be used for novel devices not previously classified by the FDA that are low or moderate risk. Except in some limited circumstances, the FDA generally will not approve a biologic that is dependent upon the use of a companion diagnostic device if the device is not contemporaneously FDA-approved or -cleared.

Post-approval Requirements

Any products manufactured or distributed pursuant to the FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements related to manufacturing, recordkeeping, and reporting, including adverse experience reporting, deviation reporting, shortage reporting, and periodic reporting, product sampling and distribution, advertising, marketing, promotion, certain electronic records and signatures, and post-approval obligations imposed as a condition of approval, such as Phase 4 clinical trials, REMS, and surveillance to assess safety and effectiveness after commercialization.

After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing annual program user fee requirements for approved products, excluding orphan products. Regulatory authorities may withdraw product approvals, require label modifications, or request product recalls, among other actions, if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Changes to the manufacturing process are strictly regulated and often require prior FDA approval or notification before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and specifications and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in production and quality control to maintain cGMP compliance.

The FDA also strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. A company can make only those claims relating to a product that are approved by the FDA. Physicians, in their independent professional medical judgment, may prescribe legally available products for unapproved indications that are not described in the product's labeling and that differ from those tested and approved by the FDA. Biopharmaceutical companies, however, are required to promote their products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability, including, but not limited to, criminal and civil penalties under the FDCA and False Claims Act, exclusion from participation in federal healthcare programs, mandatory compliance programs under corporate integrity agreements, suspension and debarment from government contracts, and refusal of orders under existing government contracts.

In addition, the distribution of prescription biopharmaceutical samples is subject to the Prescription Drug Marketing Act (the "PDMA"), which regulates the distribution of samples at the federal level. Both the PDMA and state laws limit the distribution of prescription biopharmaceutical product. Certain reporting related to samples is also required samples and impose requirements to ensure accountability in distribution. Free trial or starter prescriptions provided through pharmacies are also subject to regulations under the Medicaid Drug Rebate Program and potential liability under anti-kickback and false claims laws.

Moreover, the enacted Drug Quality and Security Act ("DQSA"), imposes obligations on sponsors of biopharmaceutical products related to product tracking and tracing. Among the requirements of this legislation, sponsors are required to provide certain information regarding the products to individuals and entities to which product ownership is transferred, are required to label products with a product identifier, and are required to keep certain records regarding the product. The transfer of information to subsequent product owners by sponsors is also required to be done electronically. Sponsors must also verify that purchasers of the sponsors' products are appropriately licensed. Further, under this legislation, manufactures have product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences of death to humans, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death. Similar requirements additionally are and will be imposed through this legislation on other companies within the biopharmaceutical product supply chain, such as distributors and dispensers, as well as certain sponsor licensees and affiliates.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements before or after approval, may result in significant regulatory actions. Such actions may include refusal to approve pending applications, license or approval suspension or revocation, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, cyber letters, modification of promotional materials or labeling, provision of corrective information, imposition of post-market requirements including the need for additional testing, imposition of distribution or other restrictions under a REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, suspension and debarment from government contracts, and refusal of orders under existing government contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties, including fines and imprisonment, and adverse publicity, among other adverse consequences.

Additional controls for biologics

To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing the results of all the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products before releasing the lots for distribution by the manufacturer.

In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Certain gene therapy studies are also subject to the National Institutes of Health's Guidelines for Research Involving Recombinant DNA Molecules, ("NIH Guidelines"). The NIH Guidelines include the review of the study by an IBC. The IBC assesses the compliance of the research with the NIH Guidelines, assesses the safety of the research and identifies any potential risk to public health or the environment. The FDA has also issued guidance with respect to gene therapies, such as guidance concerning preclinical studies, chemistry manufacturing and controls, potency testing, and long-term patient and clinical study subject follow up and regulatory reporting. The FDA further issued a draft guidance specific to the development of gene therapy products for neurodegenerative diseases as such products may face special challenges.

Patent Term Restoration

If approved, biologic products may also be eligible for periods of U.S. patent term restoration. If granted, patent term restoration extends the patent life of a single unexpired patent, that has not previously been extended, for a maximum of five years. The total patent life of the product with the extension also cannot exceed fourteen years from the product's approval date. Subject to the prior limitations, the period of the extension is calculated by adding half of the time from the effective date of an IND to the initial submission of a marketing application, and all the time between the submission of the marketing application and its approval. This period may also be reduced by any time that the applicant did not act with due diligence.

Anti-Kickback Provisions and other Fraud and Abuse Requirements

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs, in whole or in part. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. The term "remuneration" has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between biopharmaceutical industry members on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. There are certain statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly, and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances.

The Department of Health and Human Services ("HHS") recently promulgated a regulation with respect to the safe harbors that is effective in two phases. First, the regulation excludes from the definition of "remuneration" limited categories of (a) Pharmacy Benefit Manager ("PBM") rebates or other reductions in price to a plan sponsor under Medicare Part D or a Medicaid Managed Care Organization plan reflected in point-of sale reductions in price and (b) PBM service fees. Second, as amended, effective January 1, 2023, the regulation expressly provides that rebates to plan sponsors under Medicare Part D either directly to the plan sponsor under Medicare Part D, or indirectly through a pharmacy benefit manager will not be protected under the anti-kickback discount safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, including purchases of products paid by federal healthcare programs, the statute has been violated. The Patient Protection and Affordable Care Act, of 2010, as amended, (the "ACA") modified the intent requirement under the Anti-Kickback Statute to a stricter standard, such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it to have committed a violation. In addition, the ACA also provided that a violation of the federal Anti-Kickback Statute is grounds for the government or a whistleblower to assert that a claim for payment of items or services resulting from such violation constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

Federal civil false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or avoiding, decreasing, or concealing an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. The civil False Claims Act has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion of off-label uses not expressly approved by the FDA in a product's label, and allegations as to misrepresentations with respect to products, contract requirements, and services rendered. In addition, private payers have been filing follow-on lawsuits alleging fraudulent misrepresentation, although establishing liability and damages in these cases is more difficult than under the FCA. Intent to deceive is not required to establish liability under the civil False Claims Act. Rather, a claim may be false for deliberate ignorance of the truth or falsity of the information provided or acts in reckless disregard of the truth or falsity of that information. Civil False Claims Act actions may be brought by the government or may be brought by private individuals on behalf of the government, called "qui tam" actions. If the government decides to intervene in a qui tam action and prevails in the lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone. The civil FCA provides for treble damages and a civil penalty for each false claim, such as an invoice or pharmacy claim for reimbursement, which can aggregate into millions of dollars. For these reasons, since 2004, False Claims Act lawsuits against biopharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, as much as $3.0 billion, regarding certain sales practices and promoting off label uses. Civil False Claims act liability may further be imposed for known Medicare or Medicaid overpayments, for example, overpayments caused by understated rebate amounts, that are not refunded within 60 days of discovering the overpayment, even if the overpayment was not caused by a false or fraudulent act. In addition, conviction, or civil judgment for violating the FCA may result in exclusion from federal health care programs, and suspension and debarment from government contracts, and refusal of orders under existing government contracts. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer.

The government may further prosecute conduct constituting a false claim under the criminal False Claims Act. The criminal False Claims Act prohibits the making or presenting of a claim to the government knowing such claim to be false, fictitious, or fraudulent and, unlike the civil False Claims Act, requires proof of intent to submit a false claim.

The civil monetary penalties statute is another potential statute under which biopharmaceutical companies may be subject to enforcement. Among other things, the civil monetary penalties statue imposes fines against any person who is determined to have knowingly presented, or caused to be presented, claims to a federal healthcare program that the person knows, or should know, is for an item or service that was not provided as claimed or is false or fraudulent.

Payment or reimbursement of prescription therapeutics by Medicaid or Medicare requires sponsors to submit certified pricing information to Centers of Medicare and Medicaid Services ("CMS"). The Medicaid Drug Rebate statute requires sponsors to calculate and report price points, which are used to determine Medicaid rebate payments shared between the states and the federal government and Medicaid payment rates for certain therapeutics. For therapeutics paid under Medicare Part B, sponsors must also calculate and report their Average Sales Price, which is used to determine the Medicare Part B payment rate. In addition, therapeutics covered by Medicaid are subject to an additional inflation penalty which can substantially increase rebate payments. For products approved under a BLA (including biosimilars), the Veterans Health Care Act, (the "VHCA"), requires sponsors to calculate and report to the Veterans Administration, or VA, a different price called the Non-Federal Average Manufacturing Price, which is used to determine the maximum price that can be charged to certain federal agencies, referred to as the Federal Ceiling Price, ("FCP"). Like the Medicaid rebate amount, the FCP includes an inflation penalty. A Department of Defense regulation requires sponsors to provide this discount on therapeutics dispensed by retail pharmacies when paid by the TRICARE Program. All these price reporting requirements create risk of submitting false information to the government, potential FCA liability and exclusion from certain of these programs.

The VHCA also requires sponsors of covered therapeutics participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered therapeutics must be sold to certain federal agencies at FCP. This necessitates compliance with applicable federal procurement laws and regulations, including submission of commercial sales and pricing information, and subjects companies to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires sponsors participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics under the 340B program based on the sponsor's reported Medicaid pricing information. The 340B program has its own regulatory authority to impose sanctions for non-compliance and adjudicate overcharge claims against sponsors by the purchasing entities and, impose civil monetary penalties for instances of overcharging.

The federal Health Insurance Portability and Accountability Act of 1996, ("HIPAA"), also created federal criminal statutes that prohibit, among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, a healthcare benefit program, regardless of whether the payor is public or private, in connection with the delivery or payment for health care benefits, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. Additionally, the ACA amended the intent requirement of certain of these criminal statutes under HIPAA so that a person or entity no longer needs to have actual knowledge of the statute, or the specific intent to violate it, to have committed a violation.

In addition, as part of the ACA, the federal government enacted the Physician Payment Sunshine Act. Manufacturers of drugs biologics and devices for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program (with certain exceptions) are required to annually report to CMS payments and transfers of value made to or at the request of covered recipients, such as, but not limited to, physicians, physician assistants, nurse practitioners, clinical nurse specialists, and certified registered nurse anesthetists and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family. Payments made to physicians and certain research institutions for clinical trials are also included within this law. Reported information is made publicly available by CMS. Failure to submit required information may result in civil monetary penalties. If not preempted by this federal law, several states currently also require reporting of marketing and promotion expenses, as well as gifts and payments to healthcare professionals. State legislation may also prohibit various other marketing related activities or require the public posting of information. Certain states also require companies to implement compliance programs.

Further, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, ("HITECH Act"), and their respective implementing regulations impose certain requirements on covered entities relating to the privacy, security, and transmission of individually identifiable health information, known as protected health information. Among other things, the HITECH Act, through its implementing regulations, makes HIPAA's security standards and certain privacy standards directly applicable to business associates, defined as a person or organization, other than a member of a covered entity's workforce, that creates, receives, maintains, or transmits protected health information on behalf of a covered entity for a function or activity regulated by HIPAA. The HITECH Act also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates, and individuals, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, other federal and state laws, such as the California Consumer Privacy Act, may govern the privacy and security of health and other information in certain circumstances, many of which differ from each other in significant ways and may not be preempted by HIPAA, thus complicating compliance efforts.

Many states have also adopted laws similar to each of the above federal laws, which may be broader in scope and apply to items or services reimbursed by any third-party payor, including commercial insurers. Certain state laws also regulate sponsors' use of prescriber-identifiable data. Certain states also require implementation of commercial compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments or the provision of other items of value that may be made to healthcare providers and other potential referral sources; impose restrictions on marketing practices; or require sponsors to track and report information related to payments, gifts, and other items of value to physicians and other healthcare providers. Recently, states have enacted or are considering legislation intended to make drug prices more transparent and deter significant price increases. These laws may affect our future sales, marketing, and other promotional activities by imposing administrative and compliance burdens.

If our operations are found to be in violation of any of the laws or regulations described above or any other laws that apply to us, we may be subject to penalties or other enforcement actions, including criminal and significant civil monetary penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, corporate integrity agreements, suspension and debarment from government contracts, and refusal of orders under existing government contracts, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our business.

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party, or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Coverage, Pricing and Reimbursement

The containment of healthcare costs has become a priority of federal, state, and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payers and independent non-profit healthcare research organizations such as the Institute for Clinical and Economic Review are also increasingly challenging the prices charged for medical products and services and examining the medical necessity, budget-impact, and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payers do not consider a product to be cost-effective compared to other available therapies and/or the standard of care, they may not cover the product after approval as a benefit under their plans or, if they do, measures including prior authorization and step-throughs could be required, manufacturer rebates may be negotiated or required and/or the level of payment may not be sufficient to allow a company to sell its products at a profit. The U.S. federal and state governments and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products for branded prescription drugs. In this regard, for example, on November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nation payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capital Gross Domestic Product-adjusted ("GDP-adjusted") price of any non-U.S. member country of the Organization for Economic Co-operation and Development ("OECD") with a GDP per capita that is at least sixty percent of the U.S. GDP per capita. Adoption of additional healthcare reform controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

As a result, the marketability of any product which receives regulatory approval for commercial sale may suffer if the government and third-party payers choose to provide low coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on drug pricing. Coverage policies, third party reimbursement rates and drug pricing regulation may change at any time. In particular, the ACA contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to 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. Multiple other current and proposed legislative and regulatory efforts require and likely will in the future require payment of increased manufacturer rebates and implement mechanisms to reduce drug prices. Even if favorable coverage and reimbursement status is attained for one or more products that receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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 broadly in the same way 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 EU member states. The Clinical Trials Directive 2001/20/EC, as amended ("CTD") (and to be replaced by the Clinical Trial Regulation EU 536/2014) ("CTR") (it is anticipated by December 2021), provides a system for the approval of clinical trials in the European Union via (in the case of the CTD) implementation through national legislation of the member states. The CTR is directly applicable in all member states without the need for national implementation. Under this system, approval must be obtained from the competent national authority of an EU member state in which the clinical trial is to be conducted. Once the CTR comes into effect however, it will be possible within the EU to make a single harmonized electronic submission and have a single assessment process for clinical trials conducted in multiple member states. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the clinical trial application ("CTA"), which must be supported by an investigational medicinal product dossier with supporting information prescribed by the CTD and corresponding national laws of the member states and further detailed in applicable guidance documents. In the case of Advanced Therapy Investigational Medical Products ("ATIMPs") consisting of or containing Genetically Modified Organisms ("GMOs"), as is the case for uniQure's products, an additional approval for the environmental and biosafety aspects of the use and release of the GMO is required by the GMO competent authorities and GMO directives have been implemented in different ways by Member States; either following the directive for "Contained use" (Directive 2009/41/EC) or "deliberate release" (Directive2001/18/EC). This results in some EU member states, the GMO application must be approved before the Clinical Trial Application (CTA) is submitted, in some after approval of the CTA and in some parallel.

The sponsor of a clinical trial, or its legal representative, must be based in the European Economic Area ("EEA"). European regulators and ethics committees also require the submission of adverse event reports during a study and a copy of the final study report. When the CTR comes into force member states may dispense with the requirement for a legal representative for a non-EU resident sponsor provided there is a contact person based in the EEA.

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—EU 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, and advanced therapy medicinal products as defined in Regulation (EC) No 1394/2007, as amended. 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, as amended, also fall within the mandatory scope of the centralized procedure. Because of our focus on gene therapies, which fall within the category of advanced therapy medicinal products ("ATMPs") and orphan indications, our products and product candidates will need to go through the centralized procedure.

In the marketing authorization application ("MAA") the applicant must properly and sufficiently demonstrate the quality, safety, and efficacy of the drug. Guidance on the factors that the EMA will consider in relation to the development and evaluation of ATMPs have been issued and include, among other things, the preclinical studies required to characterize ATMPs; 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 of ATMPs. Although these guidelines are not legally binding, we believe that our compliance will effectively be necessary to gain and maintain approval for any of our product candidates. The maximum timeframe for the evaluation of an MAA under the centralized procedure is 210 days after receipt of a valid application subject to clock stops during which the applicant deals with EMA questions.

Market access can be expedited through the grant of conditional authorization for a medicine that may fulfil unmet needs which may be granted provided that the benefit-risk balance of the product is positive. The benefit-risk balance is likely to be positive if the applicant can provide comprehensive data and the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data. Such authorizations are valid for one year and can be renewed annually. The holder will be required to complete specific obligations (ongoing or new studies, and in some cases additional activities) with a view to providing comprehensive data confirming that the benefit-risk balance is positive. Once comprehensive data on the product have been obtained, the marketing authorization may be converted into a standard marketing authorization (not subject to specific obligations). Initially, this is valid for 5 years, but can be renewed for unlimited validity. Applicants for conditional authorizations can benefit from early dialogue with EMA through scientific advice or protocol assistance and discuss their development plan well in advance of the submission of a marketing-authorization application. Other stakeholders (e.g., health technology assessment bodies) can be included.

In addition, the priority medicines (PRIME) scheme for medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options based on early clinical data, is intended to support the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. Early dialogue and scientific advice also ensure that patients only participate in trials designed to provide the data necessary for an application, making the best use of limited resources.

The European Union 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 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 eight-year period from when the first placement of the product on the EEA market. 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 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 can 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, preclinical tests, and clinical trials. The EMA has also issued guidelines for a comprehensive comparability exercise for biosimilars, and for specific classes of biological products.

Under Regulation (EC) No 141/2000 article 3 as amended (Orphan Drug Regulation, ("ODR")) a product can benefit from orphan drug status if 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 Community (EC) when the application is made. The principal benefit of such status is 10 years' market exclusivity once they are approved preventing the subsequent approval of similar medicines with similar indications although this may be reduced to six years under certain circumstances including if the product is sufficiently profitable not to justify maintenance of market exclusivity.

Additional rules apply to medicinal products for pediatric use under Regulation (EC) No 1901/2006, as amended. 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 an orphan medicinal product pursuant to the ODR. 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, as amended, to twelve years subject to the conditions applicable to orphan drugs.

Manufacturing and promotion

Pursuant to Commission 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 a prohibition on direct-to-consumer advertising. All medicines advertising must be consistent with the product's approved summary of products characteristics, factual, accurate, balanced and not misleading. Advertising of medicines pre-approval or off-label is prohibited. Some jurisdictions require that all promotional materials for prescription medicines be subjected to either prior internal or regulatory review & approval.

Other Regulatory Requirements

A holder of a marketing authorization for a medicinal product is legally obliged to fulfill several obligations by virtue of its status as a marketing authorization holder ("MAH"). The MAH can delegate the performance of related tasks to third parties, such as distributors or marketing collaborators, 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, to 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 their 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.
- *Medical Affairs/Scientific Service.* MAHs are required to disseminate scientific and medical information on their 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 collaborator 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. In respect of the public systems, reimbursement for standard drugs is determined by guidelines established by the legislature or responsible national authority. 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 determine the prices for their medicines but monitor and control company profits and may limit or restrict reimbursement and can include retrospective rebates to the Government. 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 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 or agreements on reimbursement may apply. Recently, a process has been formalized that allows sponsors to receive parallel advice from EMA and relevant national health technology assessment ("HTA") bodies for pivotal clinical studies designed to support marketing approval. This process was followed for etranacogene dezaparvovec.

Orphan Drug Regulation

We have been granted orphan drug exclusivity for etranacogene dezaparvovec for the treatment of hemophilia B as well as for AMT-130 for the treatment of Huntington's disease subject to the conditions applicable to orphan drug exclusivity 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.

If an EU-wide community marketing authorization in respect of an orphan drug is granted pursuant to Regulation (EC) No 726/2004, as amended, 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, in respect of 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, which concepts have been expanded upon in subsequent Commission guidance. 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.

Human Capital Resources

As of December 31, 2020, we had a total of 332 employees, 162 of whom are based in Amsterdam, The Netherlands, and 170 in Lexington, Massachusetts, United States of America. As of December 31, 2020, 62 of our employees had an M.D. or Ph.D. degree, or the foreign equivalent. During 2017, we established a works council in the Netherlands. None of our employees are subject to collective bargaining or other labor organizations. We believe that we have good relations with all our employees and with the works council in the Netherlands.

Our values are to:

- Be passionate about the patient;
- Act with integrity and respect;
- Take ownership and act with urgency;
- Collaborate for success;
- Innovate every day; and
- Focus relentlessly on quality.

Development of our culture is reflected as part of our annual corporate goals. We invest in numerous learning opportunities focused on individual, management and team development and other initiatives to support our employees and build our culture.

Corporate Information

uniQure B.V. (the "Company") was incorporated on January 9, 2012 as a private company with limited liability (besloten vennootschap met beperkte aansprakelijkheid) under the laws of the Netherlands. We are a leader in the field of gene therapy and seek to deliver to patients suffering from rare and other devastating diseases single treatments with potentially curative results. Our business was founded in 1998 and was initially operated through our predecessor company, Amsterdam Molecular Therapeutics Holding N.V ("AMT"). In 2012, AMT undertook a corporate reorganization, pursuant to which uniQure B.V. acquired the entire business and assets of AMT and completed a share-for-share exchange with the shareholders of AMT. Effective February 10, 2014, in connection with the initial public offering, we converted into a public company with limited liability (naamloze vennootschap) and changed its legal name from uniQure B.V. to uniQure N.V.

We are registered in the trade register of the Dutch Chamber of Commerce (Kamer van Koophandel) under number 54385229. Our headquarters are in Amsterdam, the Netherlands, and its registered office is located at Paasheuvelweg 25a, Amsterdam 1105 BP, the Netherlands and its telephone number is +31 20 240 6000.

From our initial public offering until December 31, 2018, we were an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012. On the last business day of our second quarter in fiscal year 2018 the aggregate worldwide market value of ordinary shares held by our non-affiliate shareholders exceeded $700.0 million. As a result, as of December 31, 2018, we were considered a large accelerated filer and as a consequence lost our status as an emerging growth company.

Our website address is www.uniqure.com. We make available free of charge through our Internet website our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, and any amendments to these reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the SEC. Also available through our website's "Investors & Newsroom: Corporate Governance" page are charters for the Audit, Compensation and Nominations and Corporate Governance committees of our board of directors and our Code of Business Conduct and Ethics. We are not including the information on our website as a part of, nor incorporating it by reference into, this report.

Item 1A. Risk Factors

An investment in our ordinary shares involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes thereto, before deciding to invest in our ordinary shares. We operate in a dynamic and rapidly changing industry that involves numerous risks and uncertainties. The risks and uncertainties described below are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below actually occur, our business, financial condition, operating results, or cash flows could be materially adversely affected. This could cause the value of our securities to decline, and you may lose all or part of your investment.

Risks Related to the CSL Behring Collaboration and License Transaction

In June 2020, uniQure biopharma B.V., our wholly-owned subsidiary, entered into the CSL Behring Agreement with CSL Behring providing CSL Behring exclusive global rights to etranacogene dezaparvovec.

We and CSL Behring may be unable to close the transaction contemplated by the CSL Behring Agreement, and any delay in completing the transaction could diminish the anticipated benefits of the transaction or result in increased costs. Failure to close the transaction could adversely impact the market price of our shares as well as our business and operating results, cash flows and results of operations.

The closing of the transaction contemplated by the CSL Behring Agreement is contingent on completion of the successful review by the FTC under antitrust laws in the United States, including the expiration of the waiting period under the HSR Act by a certain date. On January 4, 2021, we received a Second Request from the FTC, the effect of which is the extension of the waiting period imposed under the HSR Act until 30 days after all parties to the CSL Behring Agreement have substantially complied with the requests (unless the waiting period is terminated earlier by the FTC or voluntarily extended by the parties). We cannot make any assurances as to the timing of the closing of the transaction or whether the transaction will be closed at all, or that, as part of the regulatory review process, additional conditions or terms will not be required.

The requirement to receive these clearances before the closing of the transaction could delay the transaction or result in an inability to complete the transaction if such clearances are not timely obtained or not obtained at all. Any delay in the completion of the transaction could diminish the anticipated benefits of the transaction, including a realization of the expected benefits of partnering, or result in additional transaction costs, loss of revenue or other effects associated with uncertainty about the transaction and could disrupt our regular operations by diverting the attention of our workforce and management team. Any such delay could also delay the timelines associated with our commercialization of etranacogene dezaparvovec, including the filing of a biologics licensing application with the FDA, and such delays could cause us to bring etranacogene dezaparvovec to market after a similar competitive product has emerged in the United States, Europe or in other markets.

We will need to fund investments into the development and preparation of the commercial launch of etranacogene dezaparvovec for as long as regulatory reviews continue. The completions of these reviews could require significant time and/or might result in modifications to or even denial of the transaction. These factors could adversely impact the cash flows and results that we are able to generate in relation to etranacogene dezaparvovec. Additionally, any uncertainty over the ability of us and CSL Behring to complete the transaction could make it more difficult for us to retain certain key employees or attract new talent or to pursue business strategies and parties with whom we have business relationships related to etranacogene dezaparvovec, either contractual or operational in nature, may experience uncertainty as to the future or desirability of such relationships and may delay or defer certain business decisions, seek alternative relationships with third parties or seek to alter their present business relationships with us.

To the extent that the market price of our ordinary shares reflects positive market assumptions that the transaction will close within a certain time frame, or at all, or that the transaction is advantageous to us, the price of such shares may decline if the transaction does not close for any reason or in a timely manner.

Risks Related to the Current COVID-19 Pandemic

Our business and operations have been, and may continue to be, materially and adversely affected by the ongoing COVID-19 pandemic.

The ongoing outbreak of COVID-19 originated in Wuhan, China, in December 2019 and has since spread to multiple countries, including the United States and the Netherlands. On March 11, 2020, the WHO declared the outbreak a pandemic. The COVID-19 pandemic is affecting the United States and global economies and has affected and may continue to affect our operations and those of third parties on which we rely. The COVID-19 pandemic has caused and may continue to cause disruptions in our raw material supply, our commercial-scale manufacturing capabilities for AAV-based gene therapies, the development of our product candidates, employee productivity and the conduct of current and future clinical trials. In addition, the COVID-19 pandemic has affected and may continue to affect the operations of the FDA, EMA, and other health authorities, which could result in delays of reviews and approvals, including with respect to our product candidates.

As evidenced by the postponement of procedures for two patients in our Phase I/II clinical study of AMT-130, the evolving COVID-19 pandemic has impacted the pace of enrollment and procedures in our clinical trials, as well as caused challenges in scheduling follow-up visits and managing other aspects of our clinical trials. We may be affected by similar delays as patients may avoid or may not be able to travel to healthcare facilities and physicians' offices unless due to a health emergency and clinical trial staff can no longer get to the clinic. Such facilities and offices have been and may continue to be required to focus limited resources on non-clinical trial matters, including treatment of COVID-19 patients, thereby decreasing availability, in whole or in part, for clinical trial services. In addition, employee disruptions and remote working environments related to the COVID-19 pandemic, and federal, state, and local public health measures designed to mitigate the spread of the virus, have impacted and could continue to negatively impact the efficiency and pace with which we work and develop our product candidates and our manufacturing capabilities. Further, while the potential economic impact brought by, and the duration of, the COVID-19 pandemic is difficult to assess or predict, the impact of the COVID-19 pandemic on global financial markets may reduce our ability to access capital, which could negatively impact our short-term and long-term liquidity. The ultimate impact of the COVID-19 pandemic is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, financing, or clinical trial activities or on healthcare systems or the global economy as a whole. However, these negative effects could have a material impact on our liquidity, capital resources, operations, and business and those of the third parties on whom we rely.

Risks Related to the Development of Our Product Candidates

None of our product candidates have been approved for commercial sale and they might never receive regulatory approval or become commercially viable. We have never generated any revenues from product sales and may never be profitable.

All our product candidates are in research or development. We have not generated any revenues from the sale of products or manufacturing of our product for a licensee and do not expect to generate any such revenue before 2022. Our lead product candidates, etranacogene dezaparvovec (also known as AMT-061) and AMT-130, and any of our other potential product candidates will require extensive preclinical and/or clinical testing, manufacture development and regulatory approval prior to commercial use. Our research and development efforts may not be successful. Even if our clinical development efforts result in positive data, our product candidates may not receive regulatory approval or be successfully introduced and marketed at prices that would permit us to operate profitably.

We may encounter substantial delays in and impediments to the progress of our clinical trials or fail to demonstrate the safety and efficacy of our product candidates.

Clinical and non-clinical development is expensive, time-consuming, and uncertain as to outcome. Our product candidates are in different stages of clinical or preclinical development, and there is a significant risk of failure or delay in each of these programs. For example, on December 21, 2020, our clinical trials of etranacogene dezaparvovec, including our HOPE-B trial, were put on clinical hold by the FDA. The clinical hold was initiated following the submission of a safety report in mid-December 2020 relating to a possibly related serious adverse event associated with a preliminary diagnosis of HCC, a form of liver cancer, in one patient in the HOPE-B trial that was treated with the etranacogene dezaparvovec in October 2019. The clinical hold could be maintained for an extended period of time or indefinitely. We cannot guarantee that any preclinical tests or clinical trials, including our clinical trials of etranacogene dezaparvovec, will be completed as planned or completed on schedule, if at all. A failure of one or more preclinical tests or clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development, as well as product candidate approval, include, but are not limited to:

- occurrence of serious adverse events associated with a product candidate that are viewed to outweigh its potential benefits;
- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations ("CROs") and clinical trial sites;
- delays in receiving regulatory authorization to conduct the clinical trials or a regulatory authority decision that the clinical trial should not proceed;
- delays in obtaining or failure to obtain required IRB and IBC approval at each clinical trial site;
- requirements of regulatory authorities, IRBs, or IBCs to modify a study in such a way that it makes the study impracticable to conduct;
- regulatory authority requirements to perform additional or unanticipated clinical trials;
- regulatory authority refusal to accept data from foreign clinical study sites;
- disagreements with regulatory authorities regarding our study design, including endpoints, our chosen indication, or our interpretation of data from preclinical studies and clinical trials or a finding that a product candidate's benefits do not outweigh its safety risks;
- delays in obtaining or failure to obtain required approvals from a DSMB or other required approvals;
- imposition of a clinical hold by regulatory agencies after an inspection of our clinical trial operations or trial sites;
- suspension or termination of clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, or other unexpected characteristics (alone or in combination with other products) of the product candidate, or due to findings of undesirable effects caused by a chemically or mechanistically similar therapeutic or therapeutic candidate;
- failure by CROs, other third parties or us to adhere to clinical trial requirements or otherwise properly manage the clinical trial process, including meeting applicable timelines, properly documenting case files, including the retention of proper case files, and properly monitoring and auditing clinical sites;
- failure of sites or clinical investigators to perform in accordance with Good Clinical Practice or applicable regulatory guidelines in other countries;
- failure of patients to abide by clinical trial requirements;
- difficulty or delays in patient recruiting into clinical trials or in the addition of new investigators;
- the impact of the COVID-19 pandemic on the healthcare system or any clinical trial sites;
- delays or deviations in the testing, validation, manufacturing, and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- the number of patients required for clinical trials of our product candidates being larger than we anticipate;
- clinical trials producing negative or inconclusive results, or our studies failing to reach the necessary level of statistical significance, requiring that we conduct additional clinical trials or abandon product development programs;
- interruptions in manufacturing clinical supply of our product candidates or issues with manufacturing product candidates that meet the necessary quality requirements;
- unanticipated clinical trial costs or insufficient funding, including to pay substantial application user fees;
- occurrence of serious adverse events or other undesirable side effects associated with a product candidate that are viewed to outweigh its potential benefits;
- disagreements with regulatory authorities regarding the interpretation of our clinical trial data and results, or the emergency of new information about or impacting our product candidates;
- determinations that there are issues with our manufacturing facility or process; or
- changes in regulatory requirements and guidance, as well as new, revised, postponed, or frozen regulatory requirements, especially in light of the change in the United States administration, that require amending or submitting new clinical protocols, undertaking additional new tests or analyses, or submitting new types or amounts of clinical data.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Such trials and regulatory review and approval take many years. It is impossible to predict when or if any of our clinical trials will demonstrate that product candidates are effective or safe in humans.

If the results of our clinical trials are inconclusive, or fail to meet the level of statistical significance required for approval or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in or altogether prevented from obtaining marketing approval for our product candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Because of the nature of the gene therapies we are developing, regulators may also require us to demonstrate long-term gene expression, clinical efficacy, and safety, which may require additional or longer clinical trials, and which may not be able to be demonstrated to the regulatory authorities' standards.

Our ability to recruit patients for our trials is often reliant on third parties, such as clinical trial sites. Clinical trial sites may not have the adequate infrastructure established to handle gene therapy products or may have difficulty finding eligible patients to enroll into a trial.

In addition, we, or any collaborators we may have may not be able to locate and enroll enough eligible patients to participate in these trials as required by the FDA, the EMA or similar regulatory authorities outside the United States and the European Union. This may result in our failure to initiate or continue clinical trials for our product candidates or may cause us to abandon one or more clinical trials altogether. Because our programs are focused on the treatment of patients with rare or orphan or ultra-orphan diseases, our ability to enroll eligible patients in these trials may be limited or slower than we anticipate considering the small patient populations involved and the specific age range required for treatment eligibility in some indications. In addition, our potential competitors, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions, may seek to develop competing therapies, which would further limit the small patient pool available for our studies. Also, patients may be reluctant to enroll in gene therapy trials where there are other therapeutic alternatives available or that may become available, which may be for various reasons including uncertainty about the safety or effectiveness of a new therapeutic such as a gene therapy and the possibility that treatment with a gene therapy therapeutic could preclude future gene therapy treatments due to the formation of antibodies following and in response to the treatment.

Any inability to successfully initiate or complete preclinical and clinical development could result in additional costs to us or impair our ability to receive marketing approval, to generate revenues from product sales or obtain regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, including changes in the vector or manufacturing process used, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. It is also possible that any such manufacturing of formulation changes may have an adverse impact on the performance of the product candidate. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may materially harm our business, financial condition, and results of operations.

Our progress in early-stage clinical trials may not be indicative of long-term efficacy in late-stage clinical trials, and our progress in trials for one product candidate may not be indicative of progress in trials for other product candidates.

Study designs and results from previous studies are not necessarily predictive of our future clinical study designs or results, and initial, top-line, or interim results may not be confirmed upon full analysis of the complete study data. Our product candidates may fail to show the required level of safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical studies. Changes to product candidates may also impact their performance in subsequent studies.

By example, our initial clinical trials in hemophilia B were conducted with AMT-060. Following these studies, we made modifications to AMT-060, substituting two nucleotides in the coding sequence for FIX. This modified product candidate is etranacogene dezaparvovec. In 2017, we announced our plans to advance etranacogene dezaparvovec, which includes an AAV5 vector carrying the FIX-Padua transgene, into a pivotal study. While we believe etranacogene dezaparvovec and AMT-060, our product candidate that was previously studied in a Phase I/II study, have been demonstrated to be materially comparable in nonclinical studies and manufacturing quality assessments, it is possible that ongoing or future clinical studies of etranacogene dezaparvovec may show unexpected differences from AMT-060. Should these differences have an unfavorable impact on clinical outcomes, or should they not have their intended effect of increasing the product candidate's FIX activity, they may adversely impact our ability to achieve regulatory approval or market acceptance of etranacogene dezaparvovec. We may also need to conduct additional or longer-term studies, which may delay regulatory submissions or approvals and which the regulatory authorities may ultimately not accept or approve.

In our Phase I/II clinical study of AMT-060, we screened patients for pre-existing anti-AAV5 antibodies to determine their eligibility for the trial. Three of the ten patients screened for the study tested positive for anti-AAV5 antibodies on reanalysis using a more sensitive antibody assay. Since we did not observe any ill-effects or correlation between the level of anti-AAV5 antibodies and clinical outcomes, patients who have anti-AAV5 antibodies are permitted to enroll in our planned pivotal study of etranacogene dezaparvovec. Since we only have been able to test a limited number of patients and have limited clinical and pre-clinical data, it is possible that ongoing or future clinical studies may not confirm these results, and if so, negatively impact the outcome of our study.

In advance of treating patients in the pivotal study of etranacogene dezaparvovec, we conducted a short study to confirm the dose expected to be used in the pivotal trial. The dose-confirmation study enrolled three patients, who were administered a single dose of $2x10^{13}$ gc/kg. We have relied on the short-term data from this study, including FIX activity and safety outcomes during the weeks following administration of etranacogene dezaparvovec, to confirm the dose to be used in the pivotal study. Following the results of this study, our Data Monitoring Committee confirmed the dose of $2x10^{13}$ gc/kg for administration in the pivotal study. Given the limited number of patients and short follow-up period, data from this study may differ materially from the future results of our planned pivotal study of etranacogene dezaparvovec.

A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials even after achieving promising results in early-stage clinical trials. If a larger population of patients does not experience positive results during clinical trials, if these results are not reproducible or if our products show diminishing activity over time, our product candidates may not receive approval from the FDA or EMA. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit, or prevent regulatory approval. In addition, we may encounter regulatory delays or rejections because of many factors, including changes in regulatory policy during the period of product development. Failure to confirm favorable results from earlier trials by demonstrating the safety and effectiveness of our products in later-stage clinical trials with larger patient populations could have a material adverse effect on our business, financial condition, and results of operations.

Additionally, where there are differences in the early-stage and late-stage trials, such as the differences between AMT-060 and AMT-061, regulatory authorities may require additional or longer-term data in late-stage trials, which may delay regulatory submissions or approvals and which the regulatory authorities may ultimately not accept or approve.

Fast track product, breakthrough therapy, priority review, or RMAT designation by the FDA, or access to the PRIME scheme by the EMA, for our product candidates may not lead to faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval.

We have obtained and may in the future seek one or more of fast track designation, breakthrough therapy designation, RMAT designation, PRIME scheme access or priority review designation for our product candidates. A fast track product designation is designed to facilitate the clinical development and expedite the review of drugs intended to treat a serious or life-threatening condition and which demonstrate the potential to address an unmet medical need. 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, where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A RMAT designation is designed to accelerate approval for regenerative advanced therapies. Priority review designation is intended to speed the FDA marketing application review timeframe for drugs that treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. PRIME is a scheme provided by the EMA, similar to the FDA's breakthrough therapy designation, to enhance support for the development of medicines that target an unmet medical need.

For drugs and biologics that have been designated as fast track products, RMAT, or breakthrough therapies, or granted access to the PRIME scheme, interaction and communication between the regulatory agency and the sponsor of the trial can help to identify the most efficient path for clinical development. Sponsors of fast track products, RMAT products, or breakthrough therapies may also be able to submit marketing applications on a rolling basis, meaning that the FDA may review portions of a marketing application before the sponsor submits the complete application to the FDA, if the sponsor pays the user fee upon submission of the first portion of the marketing application and the FDA approves a schedule for the submission of the remaining sections. For products that receive a priority review designation, the FDA's marketing application review goal is shortened to six months, as opposed to ten months under standard review.

Designation as a fast track product, breakthrough therapy, RMAT, PRIME, or priority review product is within the discretion of the regulatory agency. Accordingly, even if we believe one of our product candidates meets the relevant criteria, the agency may disagree and instead determine not to make such designation. In any event, the receipt of such a designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional regulatory procedures and does not assure ultimate marketing approval by the agency. In addition, the FDA may later decide that the products no longer meet the applicable conditions for qualification as either a fast track product, RMAT, or a breakthrough therapy or, for priority review products, decide that the period for FDA review or approval will not be shortened.

We may not be successful in our efforts to use our gene therapy technology platform to build a pipeline of additional product candidates.

An element of our strategy is to use our gene therapy technology platform to expand our product pipeline and to progress these candidates through preclinical and clinical development ourselves or together with collaborators. Although we currently have a pipeline of programs at various stages of development, we may not be able to identify or develop product candidates that are safe and effective. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development. Research programs to identify new product candidates require substantial technical, financial, and human resources. We or any collaborators may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful. If we do not continue to successfully develop and commercialize product candidates based upon our technology, we may face difficulty in obtaining product revenues in future periods, which could result in significant harm to our business, results of operations and financial position and materially adversely affect our share price.

Our strategy of obtaining rights to key technologies through in-licenses may not be successful.

We seek to expand our product pipeline from time to time in part by in-licensing the rights to key technologies, including those related to gene delivery, genes, and gene cassettes. The future growth of our business will depend in significant part on our ability to in-license or otherwise acquire the rights to additional product candidates or technologies, particularly through our collaborations with academic research institutions. However, we may be unable to in-license or acquire the rights to any such product candidates or technologies from third parties on acceptable terms or at all. The in-licensing and acquisition of these technologies is a competitive area, and many more established companies are also pursuing strategies to license or acquire product candidates or technologies that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be competitors may be unwilling to license rights to us. Furthermore, we may be unable to identify suitable product candidates or technologies within our areas of focus. If we are unable to successfully obtain rights to suitable product candidates or technologies, our business, financial condition, and prospects could suffer.

Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain marketing approvals for our product candidates.

Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. The risk of cancer remains a concern for gene therapy, and we cannot assure that it will not occur in any of our planned or future clinical studies. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material.

A small number of patients have experienced serious adverse events during our clinical trials of either AMT-060 (our first-generation hemophilia B gene therapy) or etranacogene dezaparvovec. Any adverse events in our clinical trials or those conducted by other parties (even if not ultimately attributable to our product candidates), and the resulting publicity, could result in delay, a hold or termination of our clinical trials, increased governmental regulation, unfavorable public perception, failure of the medical community to accept and prescribe gene therapy treatments, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. If any of these events should occur, it may have a material adverse effect on our business, financial condition, and results of operations.

Certain of our product candidates may require medical devices for product administration and/or diagnostics, resulting in our product candidates being deemed combination products. This may result in the need to comply with additional regulatory requirements. If we are unable to meet these regulatory requirements, we may be delayed or not be able to obtain product approval.

Certain of our product candidates, such as AMT-130, require medical devices, such as a stereotactic, magnetic resonance imaging guided catheter, for product administration. Other of our product candidates may also require the use of a companion diagnostic device to confirm the presence of specific genetic or other biomarkers. This may result in our product candidates being deemed to be combination products, potentially necessitating compliance with the FDA's investigational device regulations, separate marketing application submissions for the medical device component, a demonstration that our product candidates are safe and effective when used in combination with the medical devices, cross labeling with the medical device, and compliance with certain of the FDA's device regulations. If we are not able to comply with the FDA's device regulations, if we are not able to effectively partner with the applicable medical device manufacturers, if we or any partners are not able to obtain any required FDA clearances or approvals of the applicable medical devices, or if we are not able to demonstrate that our product candidates are safe and efficacious when used with the applicable medical devices, we may be delayed in or may never obtain FDA approval for our product candidates, which would materially harm our business.

Moreover, certain of our delivery modalities, such as direct delivery of product candidates to the brain, may require significant physician ability and skill. If physicians are not able to effectively deliver our product candidates to the applicable site of action or if delivery modalities are too difficult, we may never be able to obtain approval for our product candidates, may be delayed in obtaining approval, or, following approval, physicians may not adopt our product candidates, any of which may materially harm our business.

Risks Related to Our Manufacturing

Our manufacturing facility is subject to significant government regulations and approvals. If we fail to comply with these regulations or maintain these approvals our business could be materially harmed.

Our manufacturing facility in Lexington is subject to ongoing regulation and periodic inspection by the FDA, EMA, and other regulatory bodies to ensure compliance with current cGMP. Moreover, before approving a BLA for any product candidate, the FDA will inspect our manufacturing facility and processes. Any failure to follow and document our adherence to such cGMP regulations or other regulatory requirements may lead to significant delays in the availability of products for commercial sale or clinical study, may result in the termination of or a hold on a clinical study, or may delay or prevent filing or approval of marketing applications for our products.

Failure to comply with applicable regulations could also result in the FDA, EMA, or other applicable authorities taking various actions, including levying fines and other civil penalties; imposing consent decrees or injunctions; requiring us to suspend or put on hold one or more of our clinical trials; suspending or withdrawing regulatory approvals; delaying or refusing to approve pending applications or supplements to approved applications; requiring us to suspend manufacturing activities or product sales, imports or exports; requiring us to communicate with physicians and other customers about concerns related to actual or potential safety, efficacy, and other issues involving our products; mandating or recommending product recalls or seizing products; imposing operating restrictions; and seeking criminal prosecutions, among other outcomes. Poor control of production processes can also lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of a product candidate that may not be detectable in final product testing and that could have an adverse effect on clinical studies, or patient safety or efficacy. Moreover, if our manufacturing facility is not able to follow regulatory requirements, we may need to implement costly and time-consuming remedial actions. Any of the foregoing could materially harm our business, financial condition, and results of operations.

Moreover, if we are not able to manufacture a sufficient amount of our product candidates for clinical studies or eventual commercialization, our development program and eventual commercial prospects will be harmed. If we cannot produce an adequate amount of our product candidates in compliance with the applicable regulatory requirements, we may need to contract with a third party to do so, in which case third party manufacturers may not be available or available on favorable terms. The addition of a new manufacturer may also require FDA approvals, which we may not be able to obtain.

Gene therapies are complex and difficult to manufacture. We could experience capacity, production or technology transfer problems that result in delays in our development or commercialization schedules or otherwise adversely affect our business.

The insect-cell based manufacturing process we use to produce our products and product candidates is highly complex and in the normal course is subject to variation or production difficulties. Issues with any of our manufacturing processes, even minor deviations from the normal process, could result in insufficient yield, product deficiencies or manufacturing failures that result in adverse patient reactions, lot failures, insufficient inventory, product recalls and product liability claims. Additionally, we may not be able to scale up some or all our manufacturing processes, which may result in delays in obtaining regulatory approvals or otherwise adversely affect our ability to manufacture sufficient quantities of our products.

Many factors common to the manufacturing of most biologics and drugs could also cause production interruptions, including raw materials shortages, raw material failures, growth media failures, equipment malfunctions, facility contamination, labor problems, natural disasters, disruption in utility services, terrorist activities, or cases of force majeure and acts of god (including the effects of the COVID-19 pandemic) beyond our control. We also may encounter problems in hiring and retaining the experienced specialized personnel needed to operate our manufacturing process, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our manufacturing processes or facilities could make us a less attractive collaborator for academic research institutions and other parties, which could limit our access to additional attractive development programs, result in delays in our clinical development or marketing schedules and materially harm our business.

Our use of viruses, chemicals and other hazardous materials requires us to comply with regulatory requirements and exposes us to significant potential liabilities.

Our development and manufacturing processes involve the use of viruses, chemicals, other (potentially) hazardous materials and produce waste products. Accordingly, we are subject to national, federal, state, and local laws and regulations in the United States and the Netherlands governing the use, manufacture, distribution, storage, handling, treatment, and disposal of these materials. In addition to ensuring the safe handling of these materials, applicable requirements require increased safeguards and security measures for many of these agents, including controlling access and screening of entities and personnel who have access to them, and establishing a comprehensive national database of registered entities. In the event of an accident or failure to comply with environmental, occupational health and safety and export control laws and regulations, we could be held liable for damages that result, and any such liability could exceed our assets and resources, and could result in material harm to our business, financial condition, and results of operations.

Our resources might be adversely affected if we are unable to validate our manufacturing processes or develop new processes to meet our product supply needs and obligations.

The manufacture of our AAV gene therapies, including etranacogene dezaparvovec, is complex and requires significant expertise. Even with the relevant experience and expertise, manufacturers of gene therapy products often encounter difficulties in production, particularly in scaling out and validating initial production, and ensuring that the product meets required specifications. These problems include difficulties with production costs and yields, quality control, including stability and potency of the product, quality assurance testing, operator error, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. In the past, we have manufactured certain batches of etranacogene dezaparvovec, and other product candidates, intended for nonclinical, clinical and process validation purposes that have not met all of our pre-specified quality parameters. To meet our expected future production needs and our regulatory filing timelines for etranacogene dezaparvovec, as well as other gene therapy product candidates, we will need to complete the validation of our existing manufacturing processes as well as to develop larger scale manufacturing processes. If we are unable to consistently manufacture etranacogene dezaparvovec, or other gene therapy product candidates, in accordance with our pre-specified quality parameters and applicable regulatory standards, it could adversely impact our ability to validate our manufacturing processes, to meet our production needs, to file our BLA or other regulatory submissions, to develop our other proprietary programs, to conserve our cash, or to receive financial payments pursuant to our agreements with third parties, including with CSL Behring in return for supplying etranacogene dezaparvovec following regulatory approval.

Risks Related to Regulatory Approval of Our Products

We cannot predict when or if we will obtain marketing approval to commercialize a product candidate.

The development and commercialization of our product candidates, including their design, testing, manufacture, safety, efficacy, purity, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States, the EMA, and other regulatory agencies of the member states of the European Union, and similar regulatory authorities in other jurisdictions. Failure to obtain marketing approval for a product candidate in a specific jurisdiction will prevent us from commercializing the product candidate in that jurisdiction.

The process of obtaining marketing approval for our product candidates in the United States, the European Union, and other countries is expensive and may take many years, if approval is obtained at all. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application, may decide that our data are insufficient for approval, may require additional preclinical, clinical, or other studies and may not complete their review in a timely manner. Further, any marketing approval we ultimately obtain may be for only limited indications or be subject to stringent labeling or other restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining marketing approval for any of our product candidates in the United States, the European Union, or other countries, the commercial prospects of our other product candidates may be harmed and our ability to generate revenues will be materially impaired.

The risks associated with the marketing approval process are heightened by the status of our products as gene therapies.

We believe that all our current product candidates will be viewed as gene therapy products by the applicable regulatory authorities. While there are a number of gene therapy product candidates under development, in the United States, the FDA has only approved a limited number of gene therapy products, to date. Accordingly, regulators, like the FDA, may have limited experience with the review and approval of marketing applications for gene therapy products.

Both the FDA and the EMA have demonstrated caution in their regulation of gene therapy treatments, and ethical and legal concerns about gene therapy and genetic testing may result in additional regulations or restrictions on the development and commercialization of our product candidates that are difficult to predict. The FDA and the EMA have issued various guidance documents pertaining to gene therapy products, with which we likely must comply to gain regulatory approval of any of our product candidates in the United States or European Union, respectively. The close regulatory scrutiny of gene therapy products may result in delays and increased costs and may ultimately lead to the failure to obtain approval for any gene therapy product.

Regulatory requirements affecting gene therapy have changed frequently and continue to evolve, and agencies at both the U.S. federal and state level, as well as congressional committees and foreign governments, have sometimes expressed interest in further regulating biotechnology. In the United States, there have been a number of recent changes relating to gene therapy development. By example, FDA issued a number of new guidance documents on human gene therapy development, one of which was specific to human gene therapy for hemophilia and another of which was specific to rare diseases. Moreover, the European Commission conducted a public consultation in early 2013 on the application of EU legislation that governs advanced therapy medicinal products, including gene therapy products, which could result in changes in the data we need to submit to the EMA for our product candidates to gain regulatory approval or change the requirements for tracking, handling and distribution of the products which may be associated with increased costs. In addition, divergent scientific opinions among the various bodies involved in the review process may result in delays, require additional resources, and ultimately result in rejection. The FDA, EMA, and other regulatory authorities will likely continue to revise and further update their approaches to gene therapies in the coming years. These regulatory agencies, committees and advisory groups and the new regulations and guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenues to maintain our business.

Our failure to obtain or maintain orphan product exclusivity for any of our product candidates for which we seek this status could limit our commercial opportunity, and 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.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. While certain of our product candidates have received orphan drug designation, there is no guarantee that we will be able to receive such designations in the future. The FDA may grant orphan designation to multiple sponsors for the same compound or active molecule and for the same indication. If another sponsor receives FDA approval for such product before we do, we would be prevented from launching our product in the United States for the orphan indication for a period of at least seven years unless we can demonstrate clinical superiority.

Moreover, while orphan drug designation neither shortens the development or regulatory review time, nor gives the product candidate advantages in the regulatory review or approval process, generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the relevant indication, the product is entitled to a period of market exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same indication for that period. The FDA and the EMA, however, may subsequently approve a similar drug or same drug, in the case of the United States, for the same indication during the first product's market exclusivity period if the FDA or the EMA concludes that the later drug is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care. Orphan exclusivity in the United States also does not prevent the FDA from approving another product that is considered to be the same as our product candidates for a different indication or a different product for the same orphan indication. If another product that is the same as ours is approved for a different indication, it is possible that third-party payors will reimburse for products off-label even if not indicated for the orphan condition.

Orphan drug exclusivity may be lost if the FDA or the 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. The inability to obtain or failure to maintain adequate product exclusivity for our product candidates could have a material adverse effect on our business prospects, results of operations and financial condition.

Additionally, regulatory criteria with respect to orphan products is evolving, especially in the area of gene therapy. By example, in the United States, whether two gene therapies are considered to be the same for the purpose of determining clinical superiority is subject to change, and depends on a number of factors, including the expressed transgene, the vector, and other product or product candidate features. Accordingly, whether any of our product candidates will be deemed to be the same as another product or product candidate is uncertain.

As appropriate, we intend to seek all available periods of regulatory exclusivity for our product candidates. However, there is no guarantee that we will be granted these periods of regulatory exclusivity or that we will be able to maintain these periods of exclusivity.

The FDA grants product sponsors certain periods of regulatory exclusivity, during which the agency may not approve, and in certain instances, may not accept, certain marketing applications for competing drugs. For example, biologic product sponsors may be eligible for twelve years of exclusivity from the date of approval, seven years of exclusivity for drugs that are designated to be orphan drugs, and/or a six-month period of exclusivity added to any existing exclusivity period for the submission of FDA requested pediatric data. While we intend to apply for all periods of market exclusivity that we may be eligible for, there is no guarantee that we will be granted any such periods of market exclusivity. By example, regulatory authorities may determine that our product candidates are not eligible for periods of regulatory exclusivity for various reasons, including a determination by the FDA that a BLA approval does not constitute a first licensure of the product. Additionally, under certain circumstances, the FDA may revoke the period of market exclusivity. Thus, there is no guarantee that we will be able to maintain a period of market exclusivity, even if granted. In the case of orphan designation, other benefits, such as tax credits and exemption from user fees may be available. If we are not able to obtain or maintain orphan drug designation or any period of market exclusivity to which we may be entitled, we could be materially harmed, as we will potentially be subject to greater market competition and may lose the benefits associated with programs. It is also possible that periods of exclusivity will not adequately protect our product candidates from competition. For instance, even if we receive twelve years of exclusivity from the FDA, other applicants will still be able to submit and receive approvals for versions of our product candidates through a full BLA.

If we do not obtain or maintain periods of market exclusivity, we may face competition sooner than otherwise anticipated. For instance, in the United States, this could mean that a competing biosimilar product may be able to submit an application to the FDA and obtain approval. This may require that we undertake costly and time-consuming patent litigation, to the extent available, or defend actions brought by the biosimilar applicant for declaratory judgement. If a biosimilar product does enter the market, it is possible that it could be substituted for one of our product candidates, especially if it is available at a lower price.

It is also possible that, at the time we obtain approval of our product candidates, regulatory laws and policies around exclusivities may have changed. For instance, there have been efforts to decrease the United States period of exclusivity to a shorter timeframe. Future proposed budgets, international trade agreements and other arrangements or proposals may affect periods of exclusivity.

Risks Related to Commercialization

If we are unable to successfully commercialize our product candidates or experience significant delays in doing so, our business could be materially harmed.

Our ability to generate product revenues will depend on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on many factors, including:

- closing and successful execution of our transaction with CSL Behring for the commercialization of etranacogene dezaparvovec;
- successful completion of preclinical studies and clinical trials, and other work required by regulators;
- receipt and maintenance of marketing approvals from applicable regulatory authorities;
- our ability to timely manufacture sufficient quantities of our products according to required quality specifications;
- obtaining and maintaining patent and trade secret protection and non-patent, orphan drug exclusivity for our product candidates;
- obtaining and maintaining regulatory approvals using our manufacturing facility in Lexington, Massachusetts;
- launch and commercialization of our products, if approved, whether alone or in collaboration with others;
- identifying and engaging effective distributors or resellers on acceptable terms in jurisdictions where we plan to utilize third parties for the marketing and sales of our product candidates;
- acceptance of our products, if approved, by patients, the medical community, and third-party payers;

- effectively competing with existing therapies and gene therapies based on safety and efficacy profiles;
- the strength of our marketing and distribution;
- achieve optimal pricing based on durability of expression, safety, and efficacy;
- the ultimate content of the regulatory authority approved label, including the approved clinical indications, and any limitations or warnings;
- any distribution or use restrictions imposed by regulatory authorities;
- the interaction of our products with any other medicines that patients may be taking or the restriction on the use of our products with other medicines;
- the standard of care at the time of product approval;
- the relative convenience and ease of administration of our products;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- any price concessions, rebates, or discounts we may need to provide;
- complying with any applicable post-approval requirements and maintaining a continued acceptable overall safety profile; and
- obtaining adequate reimbursement for the total patient population and each subgroup to sustain a viable commercial business model in U.S. and EU markets.

By example, even if our product candidates are approved, they may be subject to limitations that make commercialization difficult. There may be limitations on the indicated uses and populations for which the products may be marketed. They may also be subject to other conditions of approval, may contain significant safety warnings, including boxed warnings, contraindications, and precautions, may not be approved with label statements necessary or desirable for successful commercialization, or may contain requirements for costly post-market testing and surveillance, or other requirements, including the submission of a risk evaluation and mitigation strategy, or REMS, to monitor the safety or efficacy of the products. Failure to achieve or implement any of the above elements could result in significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

The affected populations for our gene therapies may be smaller than we or third parties currently project, which may affect the size of our addressable markets.

Our projections of the number of people who have the diseases we are seeking to treat, as well as the subset of people with these diseases who have the potential to benefit from treatment with our therapies, are estimates based on our knowledge and understanding of these diseases. The total addressable market opportunities for these therapies will ultimately depend upon many factors, including the diagnosis and treatment criteria included in the final label, if approved for sale in specified indications, acceptance by the medical community, patient consent, patient access and product pricing and reimbursement.

Prevalence estimates are frequently based on information and assumptions that are not exact and may not be appropriate, and the methodology is forward-looking and speculative. The use of such data involves risks and uncertainties and is subject to change based on various factors. Our estimates may prove to be incorrect and new studies may change the estimated incidence or prevalence of the diseases we seek to address. The number of patients with the diseases we are targeting may turn out to be lower than expected or may not be otherwise amenable to treatment with our products, reimbursement may not be sufficient to sustain a viable business for all sub populations being studied, or new patients may become increasingly difficult to identify or access, any of which could adversely affect our results of operations and our business.

The addressable markets for AAV-based gene therapies may be impacted by the prevalence of neutralizing antibodies to the capsids, which are an integral component of our gene therapy constructs. Patients that have pre-existing antibodies to a particular capsid may not be eligible for administration of a gene therapy that includes this particular capsid. For example, etranacogene dezaparvovec, our gene therapy candidate for hemophilia B patients, incorporates an AAV5 capsid. In our Phase I/II clinical study of AMT-060, we screened patients for pre-existing anti-AAV5 antibodies to determine their eligibility for the trial. Three of the ten patients screened for the study tested positive for anti-AAV5 antibodies on reanalysis. Although we did not observe any ill-effects or correlation between the level of anti-AAV5 antibodies and clinical outcomes in these three patients, suggesting that patients who have anti-AAV5 antibodies may still be eligible for AAV5-based gene therapies, since we only have been able to test a limited number of patients and have limited clinical and pre-clinical data, we do not know if future clinical studies will confirm these results. This may limit the addressable market for etranacogene dezaparvovec and any future revenues derived from the sale of the product, if approved.

Any approved gene therapy we seek to offer may fail to achieve the degree of market acceptance by physicians, patients, third party payers and others in the medical community necessary for commercial success.

Doctors may be reluctant to accept a gene therapy as a treatment option or, where available, choose to continue to rely on existing treatments. The degree of market acceptance of any of our product candidates that receive marketing approval in the future will depend on many factors, including:

- the efficacy and potential advantages of our therapies compared with alternative treatments;
- our ability to convince payers of the long-term cost-effectiveness of our therapies and, consequently, the availability of third-party coverage and adequate reimbursement;
- the cost of treatment with gene therapies, including ours, in comparison to traditional chemical and small-molecule treatments;
- the limitations on use and label requirements imposed by regulators;
- the convenience and ease of administration of our gene therapies compared with alternative treatments;
- the willingness of the target patient population to try new therapies, especially a gene therapy, and of physicians to administer these therapies;
- the strength of marketing and distribution support;
- the prevalence and severity of any side effects;
- limited access to site of service that can perform the product preparation and administer the infusion; and
- any restrictions by regulators on the use of our products.

A failure to gain market acceptance for any of the above reasons, or any reasons at all, by a gene therapy for which we receive regulatory approval would likely hinder our ability to recapture our substantial investments in that and other gene therapies and could have a material adverse effect on our business, financial condition, and results of operation.

If we are unable to expand our commercialization capabilities or enter into agreements with third parties to market and sell any of our product candidates for which we obtain marketing approval, we may be unable to generate any product revenue.

To successfully commercialize any products that may result from our development programs, we need to continue to expand our commercialization capabilities, either on our own or with others. The development of our own market development effort is, and will continue to be, expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability.

We may enter into collaborations regarding our other product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing, and sales operations to recruit, hire, train and retain marketing and sales personnel. We also may face competition in any search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected, and our business may suffer.

We focus our research and product development on treatments for severe genetic and orphan diseases. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, the EU and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, any of which could adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive other potential products less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment, especially in certain degenerative conditions, could diminish the therapeutic benefit conferred by a gene therapy. Lastly, certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our product and product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product and product candidates, if approved, prescribing treatments that involve the use of our product and product candidates, if approved, in lieu of, or in addition to, existing treatments with which they are familiar and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any products for which we obtain marketing approval.

Ethical, legal, and social issues may reduce demand for any gene therapy products for which we obtain marketing approval.

Prior to receiving certain gene therapies, patients may be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been expressed that insurance carriers and employers may use these tests to discriminate on the basis of genetic information, resulting in barriers to the acceptance of genetic tests by consumers. This could lead to governmental authorities restricting genetic testing or calling for limits on or regulating the use of genetic testing, particularly for diseases for which there is no known cure. Any of these scenarios could decrease demand for any products for which we obtain marketing approval.

If we obtain approval to commercialize any of our product candidates outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

We expect that we will be subject to additional risks in commercializing any of our product candidates outside the United States, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements which may make it more difficult or expensive to export or import products and supplies to or from the United States;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration, and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;

- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods, and fires.

We face substantial competition, and others may discover, develop, or commercialize competing products before or more successfully than we do.

The development and commercialization of new biotechnology and biopharmaceutical products, including gene therapies, is highly competitive. We may face intense competition with respect to our product candidates, as well as with respect to any product candidates that we may seek to develop or commercialize in the future, from large and specialty pharmaceutical companies and biotechnology companies worldwide, who currently market and sell products or are pursuing the development of products for the treatment of many of the disease indications for which we are developing our product candidates. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization. In recent years, there has been a significant increase in commercial and scientific interest and financial investment in gene therapy as a therapeutic approach, which has intensified the competition in this area.

We are aware of numerous companies focused on developing gene therapies in various indications, including Applied Genetic Technologies Corp., Abbvie, Abeona Therapeutics, Adverum Biotechnologies, Ally Therapeutics, Apic Bio, Asklepios BioPharmaceutical, Astellas, AVROBIO, Bayer, Biogen, BioMarin, bluebird bio, CRISPR Therapeutics, Editas Medicine, Expression Therapeutics, Fate, Freeline Therapeutics, Generation Bio, Genethon, GlaxoSmithKline, Homology Medicines, Intellia Therapeutics, Johnson & Johnson, Krystal Biotech, Lexeo Therapeutics, LogicBio Therapeutics, Lysogene, MeiraGTx, Milo Biotechnology, Mustang Bio, Novartis, Orchard Therapeutics, Oxford Biomedica, Passage Bio, Pfizer, REGENXBIO, Renova Therapeutics, Roche, Rocket Pharmaceuticals, Sangamo Therapeutics, Sanofi, Selecta Biosciences, Sarepta Therapeutics, Sio Therapeutics, Solid Biosciences, SwanBio, Takeda, Taysha Gene Therapies, Ultragenyx, Vivet Therapeutics, and Voyager Therapeutics, as well as several companies addressing other methods for modifying genes and regulating gene expression. We may also face competition with respect to the treatment of some of the diseases that we are seeking to target with our gene therapies from protein, nucleic acid, antisense, RNAi and other pharmaceuticals under development or commercialized at pharmaceutical and biotechnology companies such as Alnylam Pharmaceuticals, Bayer, BioMarin, CSL Behring, Dicerna Pharmaceuticals, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Pfizer, Translate Bio, Roche, Sanofi, Sobi, Takeda, WaVe Life Sciences, and numerous other pharmaceutical and biotechnology firms.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than the products that we develop. Our competitors also may obtain FDA, EMA, or other regulatory approval for their products more rapidly than we do, which could result in our competitors establishing a strong market position before we are able to enter the market. A competitor approval may also prevent us from entering the market if the competitor receives any regulatory exclusivities that block our product candidates. Because we expect that gene therapy patients may generally require only a single administration, we believe that the first gene therapy product to enter the market for a particular indication will likely enjoy a significant commercial advantage and may also obtain market exclusivity under applicable orphan drug regimes.

Many of the companies with which we are competing or may compete in the future have significantly greater financial resources and expertise than we do in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If we do not achieve our projected development goals in the timeframes we announce and expect, the commercialization of our product candidates may be delayed and, as a result, our stock price may decline.

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, and other product development goals, or development milestones. These development milestones may include the commencement or completion of scientific studies, clinical trials, the submission of regulatory filings, and approval for commercial sale. From time to time, we publicly announce the expected timing of some of these milestones. All these milestones are based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones, including those that are publicly announced, the commercialization of our products may be delayed and, as a result, our stock price may decline.

Risks Related to Our Dependence on Third Parties

We rely, and expect to continue to rely, on third parties to conduct, supervise, and monitor our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or failing to comply with regulatory requirements.

We rely on third parties, study sites, and others to conduct, supervise, and monitor our preclinical and clinical trials for our product candidates and do not currently plan to independently conduct clinical or preclinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical and scientific institutions, and clinical and preclinical investigators, to conduct our preclinical studies and clinical trials.

While we have agreements governing the activities of such third parties, we have limited influence and control over their actual performance and activities. For instance, our third-party service providers are not our employees, and except for remedies available to us under our agreements with such third parties we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements or for other reasons, our trials may be repeated, extended, delayed, or terminated, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates, we may not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of 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. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected. Our third-party service providers may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting trials or other therapeutic development activities that could harm our competitive position.

Our reliance on these third-parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our trials is conducted in accordance with the general investigational plan and protocols for the trial. We must also ensure that our preclinical trials are conducted in accordance with GLPs, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with GCPs for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical and preclinical investigators, and trial sites. If we or any of our third-party service providers fail to comply with applicable GCPs or other regulatory requirements, we or they may be subject to enforcement or other legal actions, the data generated in our trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional studies.

In addition, we will be required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA or comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who may have conflicts of interest.

We cannot assure that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our trials complies with the applicable regulatory requirements. In addition, our clinical trials must be conducted with product candidates that were produced under GMP conditions. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in enforcement actions and adverse publicity.

Agreements with third parties conducting or otherwise assisting with our clinical or preclinical studies might terminate for a variety of reasons, including a failure to perform by the third parties. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative providers or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, if we need to enter into alternative arrangements, it could delay our product development activities and adversely affect our business. Though we carefully manage our relationships with our third parties, there can be no assurance that we will not encounter 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, and results of operations.

We also rely on other third parties to store and distribute our products for the clinical and preclinical trials that we conduct. Any performance failure on the part of our distributors could delay development, marketing approval, or commercialization of our product candidates, producing additional losses and depriving us of potential product revenue.

We rely on third parties for important aspects of our development programs. If these parties do not perform successfully or if we are unable to enter into or maintain key collaboration or other contractual arrangements, our business could be adversely affected.

We have in the past entered into, and expect in the future to enter into, collaborations with other companies and academic research institutions with respect to important elements of our development programs.

Any collaboration may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- we may have limited or no control over the design or conduct of clinical trials sponsored by collaborators;
- we may be hampered from entering into collaboration arrangements if we are unable to obtain consent from our licensors to enter into sublicensing arrangements of technology we have in-licensed;
- if any collaborator does not conduct the clinical trials they sponsor in accordance with regulatory requirements or stated protocols, we will not be able to rely on the data produced in such trials in our further development efforts;
- collaborators may not perform their obligations as expected;
- collaborators may also have relationships with other entities, some of which may be our competitors;
- collaborators may not pursue development and commercialization of any product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial, or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could develop, independently or with third parties, products that compete directly or indirectly with our products or product candidates, if, for instance, the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- our collaboration arrangements may impose restrictions on our ability to undertake other development efforts that may appear to be attractive to us;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights that achieves regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including over proprietary rights, contract interpretation or the preferred course of development, could cause delays or termination of the research, development or commercialization of product candidates, lead to additional responsibilities for us, delay or impede reimbursement of certain expenses or result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our rights or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may in some cases be terminated for the convenience of the collaborator and, if terminated, we could be required to expend additional funds to pursue further development or commercialization of the applicable product or product candidates.

If any collaboration does not result in the successful development and commercialization of products or if a collaborator were to terminate an agreement with us, we may not receive future research funding or milestone or royalty payments under that collaboration, and we may lose access to important technologies and capabilities of the collaboration. All the risks relating to product development, regulatory approval and commercialization described herein also apply to the activities of any development collaborators.

Risks Related to Our Intellectual Property

We rely on licenses of intellectual property from third parties, and such licenses may not provide adequate rights or may not be available in the future on commercially reasonable terms or at all, and our licensors may be unable to obtain and maintain patent protection for the technology or products that we license from them.

We currently are heavily reliant upon licenses of proprietary technology from third parties that is important or necessary to the development of our technology and products, including technology related to our manufacturing process, our vector platform, our gene cassettes, and the therapeutic genes of interest we are using. These and other licenses may not provide adequate rights to use such technology in all relevant fields of use. Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, which could have a material adverse effect on our business and financial condition.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. In addition, some of our agreements with our licensors require us to obtain consent from the licensor before we can enforce patent rights, and our licensor may withhold such consent or may not provide it on a timely basis. Therefore, we cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. In addition, if third parties who license patents to us fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

The agreements under which we license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business and financial condition.

If we fail to comply with our obligations in our intellectual property licenses with third parties, we could lose rights that are important to our business.

Our licensing arrangements with third parties may impose diligence, development and commercialization timelines, milestone payment, royalty, insurance, and other obligations on us. If we fail to comply with these obligations, our counterparties may have the right to terminate these agreements either in part or in whole, 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 these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or amended agreements with less favorable terms or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

If we are unable to obtain and maintain patent protection for our technology and products, or if the scope of the patent protection is not sufficiently broad, our ability to successfully commercialize our products may be impaired.

We rely, in part, upon a combination of forms of intellectual property, including in-licensed and owned patents to protect our intellectual property. Our success depends in a large part on our ability to obtain and maintain this protection in the United States, the European Union, and other countries, in part by filing patent applications related to our novel technologies and product candidates. Our patents may not provide us with any meaningful commercial protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. For example, patents we own currently are and may become subject to future patent opposition or similar proceedings, which may result in loss of scope of some claims or the entire patent. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

Successful challenges to our patents may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated, or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products.

The patent prosecution process is expensive, time-consuming, and uncertain, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Additionally, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, EU patent law with respect to the patentability of methods of treatment of the human body is more limited than U.S. law. Publications of discoveries in the scientific literature often lag the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after their priority date, or in some cases at all. Therefore, we cannot know with certainty whether we were the first to make the inventions or that we were the first to file for patent protection of the inventions claimed in our owned or licensed patents or pending patent applications. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the European Union, the United States or other countries may diminish the value of our patents or narrow the scope of our patent protection. Our inability to obtain and maintain appropriate patent protection for any one of our products could have a material adverse effect on our business, financial condition, and results of operations.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, or third parties may assert their intellectual property rights against us, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our owned or licensed patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, maintained in more narrowly amended form or interpreted narrowly.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, increase our operating losses, reduce available resources, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, which could have an adverse effect on the price of our ordinary shares.

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. For example, outside of the United States two of the patents we own are subject to patent opposition. If these or future oppositions are successful or if we are found to otherwise infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. We may not be able to obtain the required license on commercially reasonable terms or at all. Even if we could obtain a license, it could 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 or otherwise to cease using the relevant intellectual property. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease or materially modify some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

For example, we are aware of patents owned by third parties that relate to some aspects of our programs that are still in development. In some cases, because we have not determined the final methods of manufacture, the method of administration or the therapeutic compositions for these programs, we cannot determine whether rights under such third-party patents will be needed. In addition, in some cases, we believe that the claims of these patents are invalid or not infringed or will expire before commercialization. However, if such patents are needed and found to be valid and infringed, we could be required to obtain licenses, which might not be available on commercially reasonable terms, or to cease or delay commercializing certain product candidates, or to change our programs to avoid infringement.

If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and products could be adversely affected.

In addition to seeking patent protection, we also rely on other proprietary rights, including protection of trade secrets, know-how and confidential and proprietary information. To maintain the confidentiality of our trade secrets and proprietary information, we enter into confidentiality agreements with our employees, consultants, collaborators and other third parties who have access to our trade secrets. Our agreements with employees also provide that any inventions conceived by the individual while rendering services to us will be our exclusive property. However, we may not obtain these agreements in all circumstances, and individuals with whom we have these agreements may not comply with their terms. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. In addition, in the event of unauthorized use or disclosure of our trade secrets or proprietary information, these agreements, even if obtained, may not provide meaningful protection, particularly for our trade secrets or other confidential information. To the extent that our employees, consultants, or contractors use technology or know-how owned by third parties in their work for us, disputes may arise between us and those third parties as to the rights in related inventions.

Adequate remedies may not exist in the event of unauthorized use or disclosure of our confidential information including a breach of our confidentiality agreements. 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 in and outside of 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 or other third party, we would have no right to prevent them from using that technology or information to compete with us. The disclosure of our trade secrets or the independent development of our trade secrets by a competitor or other third party would impair our competitive position and may materially harm our business, financial condition, results of operations, stock price and prospects.

Our reliance on third parties may require us to share our trade secrets, which could increase the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we collaborate from time to time with various organizations and academic research institutions on the advancement of our gene therapy platform, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, materials transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, if we are notified in advance and may delay publication for a specified time to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements.

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 with whom they communicate, from using that technology or information to compete with us.

Risks Related to Pricing and Reimbursement

We face uncertainty related to insurance coverage of, and pricing and reimbursement for product candidates for which we may receive marketing approval.

We anticipate that the cost of treatment using our product candidates will be significant. We expect that most patients and their families will not be capable of paying for our products themselves. There will be no commercially viable market for our product candidates without reimbursement from third party payers, such as government health administration authorities, private health insurers and other organizations. Even if there is a commercially viable market, if the level of third-party reimbursement is below our expectations, most patients may not be able to afford treatment with our products and our revenues and gross margins will be adversely affected, and our business will be harmed.

Government authorities and other third-party payers, such as private health insurers and health maintenance organizations, decide for which medications they will pay and, subsequently, establish reimbursement levels. Reimbursement systems vary significantly by country and by region, and reimbursement approvals must be obtained on a country-by-country basis. Government authorities and third-party payers have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications and procedures and negotiating or requiring payment of manufacturer rebates. Increasingly, third party payers require drug companies to provide them with predetermined discounts from list prices, are exerting influence on decisions regarding the use of particular treatments and are limiting covered indications. Additionally, in the United States and some foreign jurisdictions, pending or potential legislative and regulatory changes regarding the healthcare system and insurance coverage could result in more rigorous coverage criteria and downward pressure on drug prices, and may affect our ability to profitably sell any products for which we obtain marketing approval. For example, on November 27, 2020, CMS issued an interim final rule implementing a Most Favored Nation payment model under which reimbursement for certain Medicare Part B drugs and biologicals will be based on a price that reflects the lowest per capita GDP-adjusted price of any non-U.S. member country of the OECD with a GDP per capita that is at least sixty percent of the U.S. GDP per capita.

The pricing review period and pricing negotiations for new medicines take considerable time and have uncertain results. Pricing review and negotiation usually begins only after the receipt of regulatory marketing approval, and some authorities require approval of the sale price of a product before it can be marketed. In some markets, particularly the countries of the European Union, prescription pharmaceutical pricing remains subject to continuing direct governmental control and to drug reimbursement programs even after initial approval is granted and price reductions may be imposed. Prices of medical products may also be subject to varying price control mechanisms or limitations as part of national health systems if products are considered not cost-effective or where a drug company's profits are deemed excessive. In addition, pricing and reimbursement decisions in certain countries can lead to mandatory price reductions or additional reimbursement restrictions in other countries. Because of these restrictions, any product candidates for which we may obtain marketing approval may be subject to price regulations that delay or prohibit our or our partners' commercial launch of the product in a particular jurisdiction. In addition, we or any collaborator may elect to reduce the price of our products to increase the likelihood of obtaining reimbursement approvals. If countries impose prices, which are not sufficient to allow us or any collaborator to generate a profit, we or any collaborator may refuse to launch the product in such countries or withdraw the product from the market. If pricing is set at unsatisfactory levels, or if the price decreases, our business could be harmed, possibly materially. If we fail to obtain and sustain an adequate level of coverage and reimbursement for our products by third party payers, our ability to market and sell our products could be adversely affected and our business could be harmed.

Due to the generally limited addressable market for our target orphan indications and the potential for our therapies to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

The relatively small market size for orphan indications and the potential for long-term therapeutic benefit from a single administration present challenges to pricing review and negotiation of our product candidates for which we may obtain marketing authorization. Most of our product candidates target rare diseases with relatively small patient populations. If we are unable to obtain adequate levels of reimbursement relative to these small markets, our ability to support our development and commercial infrastructure and to successfully market and sell our product candidates for which we may obtain marketing approval could be adversely affected.

We also anticipate that many or all our gene therapy product candidates may provide long-term, and potentially curative benefit, with a single administration. This is a different paradigm than that of other pharmaceutical therapies, which often require an extended course of treatment or frequent administration. As a result, governments and other payers may be reluctant to provide the significant level of reimbursement that we seek at the time of administration of our gene therapies or may seek to tie reimbursement to clinical evidence of continuing therapeutic benefit over time. Additionally, there may be situations in which our product candidates will need to be administered more than once, which may further complicate the pricing and reimbursement for these treatments. In addition, considering the anticipated cost of these therapies, governments and other payers may be particularly restrictive in making coverage decisions. These factors could limit our commercial success and materially harm our business.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses to date, expect to incur losses over the next several years and may never achieve or maintain profitability.

We had a net loss of $125.0 million in the year ended December 31, 2020, $124.2 million in 2019 and $83.3 million in 2018. As of December 31, 2020, we had an accumulated deficit of $784.7 million. To date, we have financed our operations primarily through the sale of equity securities and convertible debt, venture loans, upfront payments from our collaboration partners and, to a lesser extent, subsidies and grants from governmental agencies and fees for services. We have devoted substantially all our financial resources and efforts to research and development, including preclinical studies and clinical trials. We expect to continue to incur significant expenses and losses over the next several years, and our net losses may fluctuate significantly from quarter to quarter and year to year. Our losses will be materially impacted by the amount of license revenue that we will recognize in accordance with ASC 606 in the event of the closing of the transactions contemplated by the CSL Behring Agreement.

We anticipate that our expenses will increase substantially as we:

- Advance the clinical development of AMT-130, our Huntington’s disease gene therapy program;
- Build-out our commercial and medical affairs infrastructure and seek marketing approval for any product candidates (including etranacogene dezaparvovec in the event that the transactions contemplated by the CSL Behring Agreement do not close) that successfully complete clinical trials;

- Advance multiple research programs related to gene therapy candidates targeting liver-directed and CNS diseases;
- Continue to expand, enhance, and optimize our technology platform, including our manufacturing capabilities, next-generation viral vectors and promoters, and other enabling technologies;
- Continue to expand our employee base to support research and development, as well as general and administrative functions;
- Acquire or in-license rights to new therapeutic targets or product candidates; and
- Maintain, expand, and protect our intellectual property portfolio, including in-licensing additional intellectual property rights from third parties.

We may never succeed in these activities and, even if we do, may never generate revenues that are sufficient to achieve or sustain profitability. Our failure to become and remain profitable would depress the value of our company and could impair our ability to expand our business, maintain our research and development efforts, diversify our product offerings, or even continue our operations.

We will likely need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product development efforts or other operations which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We expect to incur significant expenses in connection with our on-going activities and that we will likely need to obtain substantial additional funding in connection with our continuing operations, in particular if the CSL Behring transaction does not close. In addition, we have based our estimate of our financing requirements on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Adequate capital may not be available to us when needed or may not be available on acceptable terms. Our ability to obtain debt financing may be limited by covenants we have made under our Second Amended and Restated Loan and Security Agreement (as amended, the "2018 Amended Facility") and our 2021 Amended Facility with Hercules and our pledge to Hercules of substantially all our assets as collateral. If we raise additional capital through the sale of equity or convertible debt securities, our shareholders' ownership interest could be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of holders of our ordinary shares.

If we raise additional funds through collaborations, strategic alliances, or marketing, distribution, or licensing arrangements with third parties, we may have to issue additional equity, relinquish valuable rights to our technologies, future revenue streams, products, or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce, or eliminate our research and development programs or any future commercialization efforts, which would have a negative impact on our financial condition, results of operations and cash flows.

Our existing and any future indebtedness could adversely affect our ability to operate our business.

As of December 31, 2020, we had $35.0 million of outstanding principal of borrowings under the 2018 Amended Facility, which following our January 2021 amendment we are required to repay in June 2023. In January 2021 we drew down a further $35.0 million from Hercules. We could in the future incur additional debt obligations beyond our borrowings from Hercules. Our existing loan obligations, together with other similar obligations that we may incur in the future, could have significant adverse consequences, including:

- requiring us to dedicate a portion of our cash resources to the payment of interest and principal, reducing money available to fund working capital, capital expenditures, research and development and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- subjecting us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and
- placing us at a disadvantage compared to our competitors that have less debt or better debt servicing options.

We may not have sufficient funds, and may be unable to arrange for additional financing, to pay the amounts due under our existing loan obligations. Failure to make payments or comply with other covenants under our existing debt could result in an event of default and acceleration of amounts due. Under the 2018 Amended Facility as well as the 2021 Amended Facility, the occurrence of an event that would reasonably be expected to have a material adverse effect on our business, operations, assets, or condition is an event of default. If an event of default occurs and the lender accelerates the amounts due, we may not be able to make accelerated payments, and the lender could seek to enforce security interests in the collateral securing such indebtedness, which includes substantially all our assets.

Risks Related to Other Legal Compliance Matters

Our relationships with customers and third-party payers will be subject to applicable anti-kickback, anti-bribery, fraud and abuse and other laws and regulations, which, if we are found in violation thereof, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payers will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with third party payers and customers may expose us to broadly applicable anti-bribery laws, including the Foreign Corrupt Practices Act, as well as fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we would be able to market, sell and distribute any products for which we obtain marketing approval.

Efforts to ensure that our business arrangements with third parties will comply with applicable laws and regulations could involve substantial costs. If our operations, or the activities of our collaborators, distributors or other third-party agents 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 of products from government funded healthcare programs and the curtailment or restructuring of our operations. The costs associated with any of these actions could be substantial and could cause irreparable harm to our reputation or otherwise have a material adverse effect on our business, financial condition, and results of operations.

We are subject to laws governing data protection in the different jurisdictions in which we operate. The implementation of such data protection regimes is complex, and should we fail to fully comply, we may be subject to penalties that may have an adverse effect on our business, financial condition, and results of operations.

Many national and state laws govern the privacy and security of health information and other personal and private information. They often differ from each other in significant ways. For instance, the EU has adopted a comprehensive data protection law called the General Data Protection Regulation (“GDPR”) that took effect in May 2018. The GDPR, together with the national legislation of the EU member states governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EU, security breach notifications, security and confidentiality of the personal data, and imposition of substantial potential fines for breaches of the data protection obligations. The GDPR imposes penalties for non-compliance of up to the greater of EUR 20.0 million or 4% of worldwide revenue. Data protection authorities from the different EU member states may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in the EU. Guidance on implementation and compliance practices are often updated or otherwise revised. The significant costs of compliance with, risk of regulatory enforcement actions under, and other burdens imposed by the GDPR as well as under other regulatory schemes throughout the world related to privacy and security of health information and other personal and private data could have an adverse impact on our business, financial condition, and results of operations.

Product liability lawsuits could cause us to incur substantial liabilities and to limit commercialization of our therapies.

We face an inherent risk of product liability related to the testing of our product candidates in human clinical trials and in connection with product sales. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we develop or sell;
- injury to our reputation and significant negative media attention;
- negative publicity or public opinion surrounding gene therapy;
- withdrawal of clinical trial participants or sites, or discontinuation of development programs;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- initiation of investigations, and enforcement actions by regulators; and product recalls, withdrawals, revocation of approvals, or labeling, marketing, or promotional restrictions;
- reduced resources of our management to pursue our business strategy; and
- the inability to further develop or commercialize any products that we develop.

Dependent upon the country where the clinical trial is conducted, we currently hold coverages ranging from EUR 500,000 to EUR 6,500,000 per occurrence and per clinical trial. Such coverage may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials. In addition, insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. In the event insurance coverage is insufficient to cover liabilities that we may incur, it could have a material adverse effect on our business, financial condition, and results of operations.

Healthcare legislative and regulatory reform measures may have a material adverse effect on our financial operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations, or financial results. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA, is a sweeping measure intended to, among other things, expand healthcare coverage within the United States, primarily through the imposition of health insurance mandates on employers and individuals and expansion of the Medicaid program. Several provisions of the law may affect us and increase certain of our costs.

In addition, other legislative changes have been adopted since the PPACA was enacted. These changes include aggregate reductions in Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, following passage of the Bipartisan Budget Act of 2018, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and, accordingly, our financial operations.

We anticipate that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and additional downward pressure on the reimbursement our customers may receive for our products. Further, there have been, and there may continue to be, judicial and Congressional challenges to certain aspects of the PPACA. For example, the U.S. Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate". Additional legislative and regulatory changes to the PPACA, its implementing regulations and guidance and its policies, remain possible in the 117th U.S. Congress and under the Biden Administration. However, it remains unclear how any new legislation or regulation might affect the prices we may obtain for any of our product candidates for which regulatory approval is obtained. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

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

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, contractors and consultants, and the large amounts of confidential information stored on those systems, make such systems vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication, and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering, and other means to affect service reliability and threaten the confidentiality, integrity, and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. The increased number of employees working remotely due to COVID-19 might increase our vulnerability to the above risk.

While we have not experienced a system failure, accident, cyber-attack, or security breach that has resulted in a material interruption in our operations to date, we have experienced and addressed recent system failures, cyber-attacks, and security breaches. In the future, such events could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets, data, or other proprietary information or other similar disruptions. Additionally, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, there can be no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business and the further development and commercialization of our product and product candidates could be delayed.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and technical staff and to attract, retain and motivate qualified personnel.

We are highly dependent on hiring, training, retaining, and motivating key personnel to lead our research and development, clinical operations, and manufacturing efforts. Although we have entered into employment agreements with our key personnel, each of them may terminate their employment on short notice. We do not maintain key person insurance for any of our senior management or employees.

The loss of the services of our key employees could impede the achievement of our research and development objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing senior management and key employees may be difficult and may take an extended period because of the limited number of individuals in our industry with the breadth and depth of skills and experience required to successfully develop gene therapy products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms.

If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Risks Related to Our Ordinary Shares

The price of our ordinary shares has been and may in the future be volatile and fluctuate substantially.

Our share price has been and may in the future be volatile. From the start of trading of our ordinary shares on the Nasdaq Global Select Market on February 4, 2014 through February 25, 2021, the sale price of our ordinary shares ranged from a high of $82.49 to a low of $4.72. The closing price on February 25, 2021, was $37.00 per ordinary share. The stock market in general and the market for smaller biopharmaceutical companies in particular, have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our ordinary shares may be influenced by many factors, including:

- the success of competitive products or technologies;
- results of clinical trials of our product candidates or those of our competitors;
- public perception of gene therapy;
- regulatory delays and greater government regulation of potential products due to adverse events;
- regulatory or legal developments in the European Union, the United States, and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- 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;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- mergers, acquisitions, licensing, and collaboration activity among our peer companies in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

Our directors, executive officers, and major shareholders, if they choose to act together, will continue to have a significant degree of control with respect to matters submitted to shareholders for approval.

Our directors, executive officers and major shareholders holding more than 5% of our outstanding ordinary shares, in the aggregate, beneficially own approximately 50.3% of our issued shares (including such shares to be issued in relation to exercisable options to purchase ordinary shares) as at December 31, 2020. As a result, if these shareholders were to choose to act together, they may be able, as a practical matter, to control many matters submitted to our shareholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could control the election of the board directors and the approval of any merger, consolidation, or sale of all or substantially all our assets. These shareholders may have interests that differ from those of other of our shareholders and conflicts of interest may arise.

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 our 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 board. These provisions include:

- staggered terms of our directors;
- a provision that our directors may only be removed at a general meeting of shareholders by a two-thirds majority of votes cast representing more than half of the issued share capital of the Company; 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 board.

We do not expect to pay dividends in the foreseeable future.

We have not paid any dividends since our incorporation. Even if future operations lead to significant levels of distributable profits, we currently intend that earnings, if any, will be reinvested in our business and that dividends will not be paid until we have an established revenue stream to support continuing dividends. Accordingly, shareholders cannot rely on dividend income from our ordinary shares and any returns on an investment in our ordinary shares will likely depend entirely upon any future appreciation in the price of our ordinary shares.

If we fail to maintain an effective system of internal controls, we may be unable to accurately report our results of operations or prevent fraud or fail to meet our reporting obligations, and investor confidence and the market price of our ordinary shares may be materially and adversely affected.

If we fail to maintain the adequacy of our internal control over financial reporting, we may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting. If we fail to maintain effective internal control over financial reporting, we could experience material misstatements in our financial statements and fail to meet our reporting obligations, which would likely cause investors to lose confidence in our reported financial information. This could in turn limit our access to capital markets, harm our results of operations, and lead to a decline in the trading price of our ordinary shares. Additionally, ineffective internal control over financial reporting could expose us to increased risk of fraud or misuse of corporate assets and subject us to potential delisting from The Nasdaq Global Select Market, regulatory investigations and civil or criminal sanctions. Our reporting and compliance obligations may place a significant strain on our management, operational and financial resources, and systems for the foreseeable future.

Risks for U.S. Holders

We have in the past qualified and in the future may qualify as a passive foreign investment company, which may result in adverse U.S. federal income tax consequence to U.S. holders.

Based on our average value of our gross assets, our cash and cash equivalents as well as the price of our shares we qualified as a passive foreign investment company ("PFIC") for U.S. federal income tax for 2016 but not in 2017, 2018, 2019 or 2020. 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 at least 75% of its gross income is passive income or on average at least 50% of the gross value of its assets is attributable to assets that produce passive income or are held to produce passive income. Passive income for this purpose generally includes dividends, interest, royalties, rents and gains from commodities and securities transactions. Our status in 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 continue to qualify as a PFIC in future taxable years. 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 biotechnology companies have been especially volatile. If we were considered a PFIC for the current taxable year or any future taxable year, a U.S. holder would be required to file annual information returns for such year, whether the U.S. holder disposed of any ordinary shares or received any distributions in respect of ordinary shares during such year. In certain circumstances a U.S. holder may be able to make certain tax elections that would lessen the adverse impact of PFIC status; however, to make such elections the U.S. holder will usually have to have been provided information about the company by us, and we do not intend to provide such information.

The U.S. federal income tax rules relating to PFICs are complex. U.S. holders are urged to consult their tax advisors with respect to the purchase, ownership and disposition of our shares, the possible implications to them of us being treated as a PFIC (including the availability of applicable election, whether making any such election would be advisable in their particular circumstances) as well as the federal, state, local and foreign tax considerations applicable to such holders in connection with the purchase, ownership, and disposition of our shares.

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

Although we now report as a U.S. domestic filer for SEC reporting purposes, we are incorporated under the laws of the Netherlands. Some of the members of our board and senior management reside outside the United States. As a result, it may not be possible for shareholders to effect service of process within the United States upon such persons or to enforce judgments 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 Board members 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. 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 Civil Procedure Code.

Therefore U.S. shareholders may not be able to enforce against us or our board members or senior management 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 and directors are governed by Dutch law and differ in some important respects from the rights and responsibilities of shareholders under U.S. law.

Although we now report as a U.S. domestic filer for SEC purposes, our corporate affairs are governed by our articles of association and by the laws governing companies incorporated in the Netherlands. The rights of our shareholders and the responsibilities of members of our board under Dutch law are different than under the laws of some U.S. jurisdictions. In the performance of their duties, our board members are required by Dutch law to consider the interests of uniQure, its shareholders, its employees, and other stakeholders and not only those of our shareholders (as would be required under the law of most U.S. jurisdictions). As a result of these considerations our directors may take action that would be different than those that would be taken by a company organized under the law of some U.S. jurisdictions.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Lexington, Massachusetts / United States

We operate an 83,998 square feet GMP qualified manufacturing facility that we lease in Lexington, Massachusetts. In November 2018, we extended and expanded the facility by leasing an additional 30,655 square feet (as from June 1, 2019 onwards) of the same building. The expanded and extended lease for the facility terminates in June 2029, and subject to the provisions of the lease, may be renewed for two subsequent five-year terms.

Amsterdam / The Netherlands

In 2016, we entered into leases for a total of approximately 111,000 square feet facility in Amsterdam. The lease for this facility terminates in 2032, with an option to extend in increments of five-year periods.

In December 2017, we entered into an agreement to sub-lease three of the seven floors of our Amsterdam facility for a ten-year term ending on December 31, 2027, with an option for the sub-lessee to extend until December 31, 2031 as well as an option that has expired to break the lease prior to December 31, 2020 subject to the lessee paying a penalty and breaking certain financial covenants. In February 2020, we amended the sub-lease agreement to take back one of the three floors effective March 1, 2020.

We believe that our existing facilities are adequate to meet current needs and that suitable alternative spaces will be available in the future on commercially reasonable terms.

Item 3. Legal Proceedings.

On or about February 22, 2021, Pavlina Konstantinova, VectorY B.V., and Forbion International Management B.V. commenced a summary proceeding in the Netherlands primarily seeking an order: (i) allowing VectorY and Dr. Konstantinova to continue their employment relationship; (ii) suspending the non-competition agreement between uniQure biopharma B.V. and Dr. Konstantinova; and (iii) precluding any monetary penalties pursuant to that non-competition agreement. The complaint also seeks payment of the costs of legal proceedings and a monetary monthly payment to Dr. Konstantinova in lieu of a promise by uniQure biopharma B.V. to release Dr. Konstantinova from her obligations under the non-competition agreement. The proceeding stems from a dispute between us, Dr. Konstantinova, VectorY and Forbion International Management B.V. over the hiring by VectorY of Dr. Konstantinova and several other former uniQure employees, which we believe is in violation of the employment agreements of those employees and involves the misappropriation of our proprietary resources. We believe that Forbion International Management B.V. is an affiliate of the Forbion group of companies that collectively own more than five percent of our outstanding ordinary shares. We are unable to express a view as to the likely outcome of this proceeding at this time.

Item 4. Mine Safety Disclosures.

Not applicable.

Part II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our ordinary shares are listed on the Nasdaq Global Select Market under the symbol "QURE". We have never paid any cash dividends on our ordinary shares, and we do not anticipate paying cash dividends in the foreseeable future. We anticipate that we will retain all earnings, if any, to support operations and to finance the growth and development of our business for the foreseeable future.

Unregistered Sales of Equity Securities

During the period covered by this Annual Report on Form 10-K, we have not issued any securities that were not registered under the Securities Act.

Issuer Share Repurchases

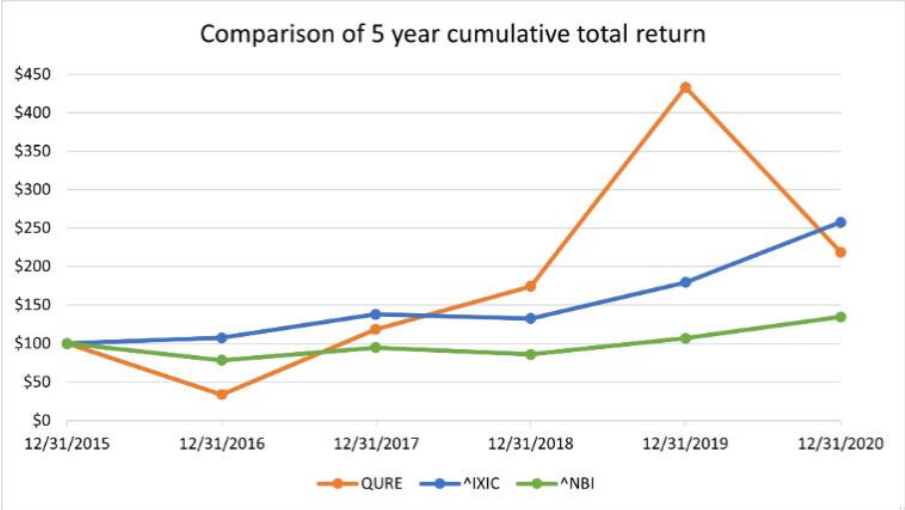
We did not make any purchases of our ordinary shares during the year ended December 31, 2020. Our affiliates made purchases of our ordinary shares as described in "Unregistered Sales of Equity Securities" above.

Holders

As of February 25, 2021, there were approximately seven holders of record of our ordinary shares. The actual number of shareholders is greater than this number of record holders, and includes shareholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include shareholders whose shares may be held in trust by other entities.

Share Performance Graph

The following graph compares the performance of our ordinary shares ("QURE") for the periods indicated with the performance of the NASDAQ Composite Index ("^IXIC") and the Nasdaq biotechnology index ("^NBI"). This graph assumes an investment of $100 after market closed December 31, 2015 in each of our ordinary shares, the NASDAQ Composite Index, and the NASDAQ Biotechnology Index, and assumes reinvestment of dividends, if any. The performance of our ordinary shares shown on the graph below is not necessarily indicative of the future performance of our ordinary shares. This graph is not "soliciting material", is not deemed "filed" with the SEC and is not to be incorporated by reference into any of our filings under the Securities Act, or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



Item 6. Selected Financial Data

Not applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following Management's Discussion and Analysis of Financial Condition and Results of Operations ("MD&A") is intended to help the reader understand our results of operations and financial condition. This MD&A is provided as a supplement to, and should be read in conjunction with, our audited consolidated financial statements and the accompanying notes thereto and other disclosures included in this Annual Report on Form 10-K, including the disclosures under "Risk Factors". Our consolidated financial statements have been prepared in accordance with generally accepted accounting principles in the United States ("U.S. GAAP") and unless otherwise indicated are presented in U.S. dollars.

Except for the historical information contained herein, the matters discussed in this MD&A may be deemed to be forward-looking statements. Forward-looking statement are only predictions based on management's current views and assumptions and involve risks and uncertainties, and actual results could differ materially from those projected or implied. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. Words such as "may," "expect," "anticipate," "estimate," "intend," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements.

Our actual results and the timing of certain events may differ materially from the results discussed, projected, anticipated, or indicated in any forward-looking statements. We caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this MD&A. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this MD&A, they may not be predictive of results or developments in future periods.

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions, or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Overview

We are a leader in the field of gene therapy, seeking to develop single treatments with potentially curative results for patients suffering from genetic and other devastating diseases. We are advancing a focused pipeline of innovative gene therapies, including product candidates for the treatment of hemophilia B, which we intend to license to CSL Behring pursuant to the CSL Behring Agreement, and Huntington's disease. We believe our validated technology platform and manufacturing capabilities provide us distinct competitive advantages, including the potential to reduce development risk, cost, and time to market. We produce our AAV-based gene therapies in our own facilities with a proprietary, commercial-scale, cGMP-compliant, manufacturing process. We believe our Lexington, Massachusetts-based facility is one of the world's most versatile gene therapy manufacturing facilities.

Business developments

Below is a summary of our recent significant business developments:

CSL Behring commercialization and license agreement

On June 24, 2020, uniQure biopharma B.V., a wholly owned subsidiary of uniQure N.V., entered into the CSL Behring Agreement with CSL Behring pursuant to which CSL Behring will receive exclusive global rights to etranacogene dezaparvovec, the Product.

Under the terms of the CSL Behring Agreement, we will receive a $450.0 million upfront cash payment upon the closing of the CSL Behring Agreement and be eligible to receive up to $1.6 billion in additional payments based on regulatory and commercial milestones. The CSL Behring agreement also provides that we will be eligible to receive tiered double-digit royalties in a range of up to a low-twenties percent of net sales of the Product based on sales thresholds.

Pursuant to the CSL Behring Agreement, we will be responsible for the completion of the HOPE-B clinical trial, manufacturing process validation, and the manufacturing supply of the Product until such time that these capabilities may be transferred to CSL Behring or its designated contract manufacturing organization. Concurrently with the execution of the CSL Behring Agreement, we and CSL Behring entered into a development and commercial supply agreement, pursuant to which, among other things, we will supply the Product to CSL Behring at an agreed-upon price. Clinical development and regulatory activities performed by us pursuant to the CSL Behring Agreement will be reimbursed by CSL Behring. CSL Behring will be responsible for global regulatory submissions and commercialization requirements for the Product.

Other than under the CSL Behring Agreement, neither we nor CSL Behring may perform any clinical trials, with the exception of trials required to extend the label or gain marketing authorization outside the United States or the European Union, for any gene therapy product, gene-editing product, or any other product comprising an AAV vector to conduct nucleotide transfer (including DNA and RNA) for the treatment, prevention, or cure of hemophilia B for a period commencing on June 24, 2020 and continuing for a period of four years following the first commercial sale of the Product in the United States, and neither we nor CSL Behring may commercialize such a product for a period commencing as of June 24, 2020 and continuing for a period of seven years following the first commercial sale of the Product in the United States. This exclusivity commitment would not bind an acquirer of us that owns or controls such a product so long as certain precautions are followed to ensure that CSL Behring's confidential information and our proprietary technology related to the Product are not used or accessed by personnel of such acquirer who are developing or commercializing such competing product.

Unless earlier terminated as described below, the CSL Behring Agreement will continue on a country-by-country basis until expiration of the royalty term in a country. The royalty term expires in a country on the later of (a) 15 years after the first commercial sale of the Product in such country, (b) expiration of regulatory exclusivity for the Product in such country and (c) expiration of all valid claims of specific licensed patents covering the Product in such country. Either we or CSL Behring may terminate the CSL Behring Agreement for the other party's material breach if such breach is not cured within a specified cure period. In addition, if CSL Behring fails to commercialize the Product in any of a group of major countries for an extended period following the first regulatory approval of the Product in any of such group of countries (other than due to certain specified reasons) and such failure has not been cured within a specified cure period, then we may terminate the CSL Behring Agreement. CSL Behring may also terminate the CSL Behring Agreement for convenience.

On November 11, 2020, the ACCC determined, pursuant to section 50 of the Competition and Consumer Act 2010 of Australia, that it will not intervene in the CSL Behring Agreement. Thus, the ACCC has completed its review of the CSL Behring Agreement, and the transactions contemplated by the CSL Behring Agreement may close from the perspective of the Australian competition authority.

On November 24, 2020, the Competition and Markets Authority in the United Kingdom (the "CMA") adopted a decision not to refer the CSL Behring Agreement for proceedings under section 33 of the Enterprise Act 2002 of the United Kingdom. The decision was made public by the CMA on January 6, 2021. Thus, the CMA has completed its review of the CSL Behring Agreement, and the transactions contemplated by the CSL Behring Agreement may close from the perspective of the United Kingdom competition authority.

On December 3, 2020, we and CSL Behring filed a premerger notification and report form under the HSR Act. On January 4, 2021, the FTC issued a Second Request under the HSR Act. The FTC similarly issued a Second Request to CSL Behring also with respect to the antitrust review of the CSL Behring Agreement. The effect of the Second Requests is to extend the waiting period imposed under the HSR Act until 30 days after all parties to the CSL Behring Agreement have substantially complied with the requests unless the waiting period is terminated earlier by the FTC or voluntarily extended by the parties.

The effectiveness of the transactions contemplated by the CSL Behring Agreement is contingent on completion of review under antitrust laws in the United States, Australia, and the United Kingdom and certain provisions of the CSL Behring Agreement will not become effective until after we receive such regulatory approvals. Regulatory approval in the United States has not occurred to date.

Closing of the transaction is expected to materially impact our profitability and cash flows. Receipt of the $450.0 million payment due on closing would extend the funding of our operations from the second half of 2022 into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules under our term loan facility by 2023). However, we expect to continue to incur losses and to generate negative cash flows beyond the fiscal year in which we would close the transaction.

BMS collaboration

We and Bristol-Myers Squibb entered into a collaboration and license agreement in May 2015. BMS initially designated four Collaboration Targets in 2015 and in accordance with the terms of the BMS CLA could have designated a fifth to tenth Collaboration Target.

In February 2019, BMS requested a one-year extension of the initial research term. In April 2019, following an assessment of the progress of this collaboration and our expanding proprietary programs, we notified BMS that we did not intend to agree to an extension of the initial research term. Accordingly, the initial four-year research term under the collaboration terminated on May 21, 2019.

On December 1, 2020, we and BMS amended the BMS CLA. Following the amendment BMS is no longer entitled to designate a fifth to tenth Collaboration Target and as such we are no longer entitled to receive an aggregate $16.5 million in target designation payments for the research, development, and regulatory milestone payments related to the fifth to tenth Collaboration Targets. For a period of one year from the effective date of the amended BMS CLA, BMS may replace up to two of the four active Collaboration Targets with two new targets in the field of cardiovascular disease. We continue to be entitled to receive up to $217.0 million for each of the four Collaboration Targets if defined milestones are achieved, as well as royalties on net sales associated with any Collaboration Target. On December 17, 2020, BMS designated one of the four Collaboration Targets as a candidate to advance into IND-enabling studies entitling the Company to receive a $4.4 million research milestone payment. The Company recorded the $4.4 million as License Revenue in the twelve-month period ended December 31, 2020.

The amended BMS CLA does not extend the initial research term. BMS may place purchase orders to provide limited services primarily related to analytical and development efforts in respect of the four Collaboration Targets. BMS may request such services for a period not to exceed the earlier of (i) the completion of all activities under a Research Plan and (ii) either (A) three years after the last replacement target has been designated by BMS during the one-year replacement period following the amended BMS CLA effective date or (B) three years if no replacement targets are designated during this one-year period and BMS continues to reimburse us for these services.

For as long as any of the four Collaboration Targets are being advanced, BMS may place a purchase order to be supplied with research, clinical and commercial supplies. Subject to the terms of the amended BMS CLA, BMS has the right to terminate the research, clinical and commercial supply relationships, and has certain remedies for failures of supply, up to and including technology transfer for any such failure that otherwise cannot be reasonably resolved. Both we and BMS may agree to a technology transfer of manufacturing capabilities pursuant to the terms of the amended BMS CLA.

The amended BMS CLA also terminated two warrants to increase BMS ownership in the Company to up to 19.9% through purchasing a specific number of our ordinary shares following the designation of a seventh and a tenth Collaboration Target, respectively. We and BMS agreed that upon the consummation of a change of control transaction of uniQure that occurs prior to the earlier of (i) December 1, 2026 and (ii) BMS' delivery of a target cessation notice for all four Collaboration Targets, we (or our third party acquirer) shall pay to BMS a one-time, non-refundable, non-creditable cash payment of $70.0 million, provided that (x) if $70.0 million is greater than five percent of the net proceeds (as contractually defined) from such change of control transaction, the payment shall be an amount equal to five percent of such net proceeds, and (y) if $70.0 million is less than one percent of such net proceeds, the change of control payment shall be an amount equal to one percent of such net proceeds. We have not consummated any change of control transaction as of December 31, 2020 that would obligate us to make a payment to BMS.

Hemophilia B program – Etranacogene dezaparvovec (AMT-061)

In August 2018, we initiated a Phase IIb dose-confirmation study of etranacogene dezaparvovec and in September 2018, we completed the dosing for that study. In February, May, July, and December 2019, and in December 2020, we presented updated data from the Phase IIb dose-confirmation study of etranacogene dezaparvovec. The most recent data that we announced from the Phase IIb study of etranacogene dezaparvovec show that all three patients experienced increasing and sustained FIX levels after a one-time administration of etranacogene dezaparvovec. Mean FIX activity was 44.2% of normal two years after administration, exceeding threshold FIX levels generally considered sufficient to significantly reduce the risk of bleeding events. The first patient achieved FIX activity of 44.7% of normal, the second patient was 51.6% of normal and the third patient was 36.3% of normal. The second and third patients had previously screen-failed and were excluded from another gene therapy study due to pre-existing neutralizing antibodies to a different AAV vector. At two years after dosing, two of the three participants remain free from bleeds and use of FIX replacement therapy. A single bleed has been reported in one participant, who has used a total of two FIX infusions (excluding surgery). All patients have remained free of prophylaxis in the two years since receiving etranacogene dezaparvovec.

In June 2018, we initiated the six-month lead-in period of our HOPE-B trial. The HOPE-B trial is a multinational, multi-center, open-label, single-arm study to evaluate the safety and efficacy of etranacogene dezaparvovec. After the six-month lead-in period, patients received a single intravenous administration of etranacogene dezaparvovec. Patients enrolled in the HOPE-B trial were tested for the presence of pre-existing neutralizing antibodies to AAV5 but not excluded from the trial based on their titers.

The primary endpoints of the study are based on the FIX activity level achieved following the administration of etranacogene dezaparvovec after 26 weeks and 52 weeks after dosing as well annualized bleed rates during the 52 weeks after dosing.

In March 2020, we completed dosing of the 54 patients in the HOPE-B trial. The targeted number of patients to be dosed per the clinical trial protocol was 50. In December 2020, we announced top-line data from the HOPE-B trial. The 26-week follow-up date from the trial showed that FIX activity in the 54 patients increased after dosing from ≤ 2% to a mean of 37.2% at 26 weeks, meeting a first primary endpoint of the HOPE-B trial. No correlation between pre-existing neutralizing antibodies and FIX activity was found in patients with neutralizing antibody titers up to 678.2, a range expected to include more than 95% of the general population; one patient with a neutralizing antibody titer of 3,212.3 did not show an increase in FIX activity. Less than 1% of the general population is expected to have neutralizing antibody titers of greater than 3,000.

During the 26-week period after dosing, 15 patients (28%) reported a total of 21 bleeding events, representing a reduction of 83% compared to the 123 bleeding events reported by 38 patients (70%) during the observational lead-in phase of the trial. Total bleeds include any bleeding event reported after the treatment of etranacogene dezaparvovec, including spontaneous, traumatic, and those associated with unrelated medical procedures, whether or not FIX treatment was required. Of the total bleeding events reported during the 26-week period after dosing, only three were classified as spontaneous bleeds requiring treatment, representing a reduction of 92% compared to the 37 such bleeding events reported during the observational lead-in phase. Mean annualized usage of FIX replacement therapy, a secondary endpoint in the clinical trial, declined by 96% during the 26-week period after dosing compared to the observational lead-in phase. Etranacogene dezaparvovec was generally well-tolerated. As of the November 2020 cut-off date, most adverse events were classified as mild (81.5%). The most common events included transaminase elevation treated with steroids per protocol (9 patients; 17%), infusion-related reactions (7 patients; 13%), headache (7 patients; 13%) and influenza-like symptoms (7 patients; 13%). Liver enzyme elevations resolved with a tapering course of corticosteroids and FIX activity remained in the mild range in the steroid treated patients. No relationship between safety and neutralizing antibody titers was observed. Based on interactions with the FDA and the EMA, we plan to incorporate FIX activity and bleeding rates at 52 weeks as additional co-primary endpoints in the study.

On December 21, 2020, our clinical trials of etranacogene dezaparvovec, including our HOPE-B trial were placed on clinical hold by the FDA. The clinical hold was initiated following the submission of a safety report in mid-December relating to a possibly related serious adverse event associated with a preliminary diagnosis of HCC, a form of liver cancer, in one patient in the HOPE-B trial that was treated with etranacogene dezaparvovec in October 2019. The patient has multiple risk factors associated with HCC, including a twenty-five-year history of HCV, HBV, evidence of non-alcoholic fatty liver disease and advanced age. Chronic infections with hepatitis B and C have been associated with approximately 80% of HCC cases.

The liver lesion was detected during a routine abdominal ultrasound conducted as part of the required study assessments in patients at one-year post dosing. A surgical resection of the lesion has occurred, and an analysis of the tissue samples was initiated in early 2021. On February 19, 2021, we reported initial results from this analysis to the FDA in accordance with pharmacovigilance requirements. We are gathering final data from these molecular analyses and will be preparing a detailed response to the FDA's clinical hold questions regarding this event. Currently, we do not have adequate data to determine a possible causal relationship, especially in the context of the other known risk factors. We currently do not anticipate any impact on our regulatory submission timelines, including the filing of a BLA.

No other cases of HCC have been reported in our clinical trials conducted in more than 67 patients in hemophilia B, with some patients dosed more than 5 years ago.

Phase I/II Clinical Trial of AMT-060

In the third quarter of 2015, we initiated a Phase I/II clinical trial of AMT-060, our first-generation hemophilia B product candidate, in patients with severe or moderately-severe hemophilia B. We enrolled five patients into a low dose cohort in the third quarter 2015. Another five patients were enrolled into a high dose cohort between March and May 2016.

In December 2020, we presented five-year follow-up data related to this Phase I/II clinical trial. All 10 patients enrolled continue to show long-term clinical benefit, including sustained increases in FIX activity, reduced usage of FIX replacement therapy, and decreased bleeding frequency. At up to five years of follow-up, AMT-060 continues to be well-tolerated, with no new treatment-related adverse events since the last reported data and no development of inhibitors during the study.

Huntington's disease program (AMT-130)

AMT-130 is our gene therapy candidate targeting Huntington's disease that utilizes an AAV vector carrying an engineered miRNA designed to silence HTT and exon 1 HTT, a potentially highly toxic protein fragment that may also contribute to disease pathology. AMT-130 comprises a recombinant AAV5 vector carrying a DNA cassette, encoding a miRNA that non-selectively lowers or knocks-down HTT and exon 1 HTT in Huntington's disease patients.

In January 2019, our IND application for AMT-130 was cleared by the FDA, thereby enabling us to initiate our planned Phase I/II clinical study. The primary objective of the study is to evaluate the safety, tolerability, and efficacy of AMT-130 at two doses.

In June 2020, we announced the completion of the first two patient procedures in the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease. These procedures occurred after a postponement that resulted from the COVID-19 pandemic and the associated states of emergency declarations in the United States. The Phase I/II protocol is a randomized, imitation surgery-controlled, double-blinded study conducted at three surgical sites, and multiple referring, non-surgical sites in the U.S. The primary objective of the study is to evaluate the safety, tolerability, and efficacy of AMT-130 at two doses.

On September 25, 2020, we announced that the independent Data Safety Monitoring Board (DSMB) overseeing the Phase I/II clinical trial of AMT-130 for the treatment of Huntington's disease has met and reviewed 90-day safety data from the first two patients enrolled in the trial. No significant safety concerns were noted to prevent further dosing.

On October 13, 2020, we announced the completion of the third and fourth patient procedures in the Phase I/II clinical trial.

On February 8, 2021, we announced that the DSMB met and reviewed the six-month safety data from the first two enrolled patients and the 90-day safety data from the next two enrolled patients in the study. No significant safety concerns were noted to prevent further dosing, and the final six patients in the first cohort are now cleared for enrollment.

Preclinical programs

Spinocerebellar Ataxia Type 3 program (AMT-150)

AMT-150 is our novel gene therapy candidate for the treatment of SCA3, also known as Machado-Joseph disease, which is caused by a CAG-repeat expansion in the ATXN3 gene that results in an abnormal form of the protein ataxin-3. AMT-150 is a one-time, intrathecally-administered, AAV gene therapy incorporating our proprietary miQURE silencing technology that is designed to halt ataxia in early manifest SCA3 patients.

At the 2019 American Academy of Neurology Annual Meeting, we presented preclinical data on AMT-150 demonstrating mechanistic proof-of-concept of the non-allele-specific ataxin-3 protein-silencing approach by using artificial miRNA candidates engineered to target the ataxin-3 gene in a SCA3 knock-in mouse model. In this proof-of-concept study, a single AMT-150 injection in the cerebrospinal fluid resulted in AAV transduction and mutant ataxin-3 lowering at the primary sites of disease neuropathology, the cerebellum (up to 53%) and the brainstem (up to 65%).

In May 2020, we presented preclinical data at the ASGCT Annual Meeting, on our gene therapy candidate SCA3. In an in vivo preclinical study, six NHP received a one-time injection of AMT-150 via the cisterna magna to assess expression and distribution. Samples taken after eight weeks showed widespread transduction of the brain and spinal cord, with the highest genome copies found in the posterior fossa and cortical regions. In other preclinical studies, researchers evaluated AMT-150 in SCA3 mouse models, as well as human iPSC-derived neurons and astrocytes, to investigate potential off-target effects of AAV5-miATXN3. The iPSC-derived cell cultures, which were derived from two SCA3 patients, represent the most disease-relevant cell type for therapeutic targeting of AMT-150. A clear dose-dependent expression of miATXN3 was observed in the iPSC-derived neurons and astrocytes transduced with AMT-150. Mature miATXN3 molecules were also associated with extracellular vesicles that strongly correlated with the dose and miATXN3 expression, suggesting the potential therapeutic spread of the engineered miATXN3. Additionally, AMT-150 demonstrated ATXN3 knockdown in human neurons and various SCA3 mouse models with subsequent neuropathology improvement.

In September 2020, we initiated a safety and toxicology study of AMT-150 in NHP.

Fabry disease program (AMT-190)

AMT-190 is our novel gene therapy candidate for the treatment of Fabry disease. AMT-190 is a one-time, IV-administered, AAV5-based gene therapy.

In September 2020, we selected a lead gene therapy candidate (AMT-190) for the treatment of Fabry disease to advance into IND-enabling studies. The lead candidate is a one-time administered AAV5 gene therapy incorporating the α-galactosidase A (GLA) transgene. In preclinical studies comparing multiple product candidates, including constructs incorporating a modified alpha-N-acetylgalactosaminidase transgene (modNAGA), AMT-190 demonstrated the most robust and sustained increases in GLA activity.

Hemophilia A program (AMT-180)

In June 2020, we announced that we plan to de-prioritize our research program of AMT-180 for patients with hemophilia A, as part of our effort to focus on those gene therapy programs that have the greatest potential to improve patients' lives and generate long-term value for shareholders.

Term loan facility

As of December 31, 2020, a $35.0 million term loan was outstanding in accordance with the 2018 Amended Facility between us and Hercules.

On January 29, 2021 we and Hercules entered into the 2021 Amended Facility. Pursuant to the 2021 Amended Facility, Hercules agreed to the 2021 Term Loan, increasing the aggregate principal amount of the term loan facility from $35.0 million to up to $135.0 million. On January 29, 2021 we drew down $35.0 million of the 2021 Term Loan. We may draw down the remaining $65.0 million under the 2021 Term Loan in a series of one or more advances of not less than $20.0 million each until December 15, 2021. Advances under the 2021 Term Loan bear interest at a rate equal to the greater of (i) 8.25% or (ii) 8.25% plus the prime rate, less 3.25% per annum. The principal balance and all accrued but unpaid interest on advances under the 2021 Term Loan is due on June 1, 2023, which date may be extended by us by up to two twelve-month periods. Advances under the 2021 Term Loan may not be prepaid until six months after the Closing Date, following which we may prepay all such advances without charge.

In addition to the 2021 Term Loan, the amendment also extends the interest only payment period of the previously funded $35.0 million term loan from January 1, 2022 to June l, 2023. End of term charges in respect of advances under the 2021 Term Loan range from 1.65% to 6.85%, depending on the maturity date.

COVID-19 measures

Starting March 2020, we implemented measures to address the impact of COVID-19 on our business. We mandated a work-from-home policy for all non-essential employees at our Amsterdam and Lexington facilities when the pandemic began. We implemented a series of protocols governing the operations of our Lexington facility to comply with the requirements of the various orders and guidance from the Commonwealth of Massachusetts and other related orders, guidance, laws, and regulations. We supported our employees in setting up a healthy and efficient remote working environment. In conjunction with implementing this policy, we accelerated the roll-out of several information technology security measures such as dual factor authentication, to address the increased risks that to which we might be exposed as a result of remote working conditions. In addition, we conducted awareness training around cybersecurity for critical functions involved in making payments to vendors such as finance and supply chain. We continue to monitor local government rules and recommendations and office protocols will be aligned with these rules and recommendations.

We conduct frequent status video-meetings of local management at our two sites as well as leadership-team video meetings to implement these measures and to monitor the evolving situation. In addition, we inform our employees through periodic newsletters and have organized virtual local and global townhalls to share information and provide direction and support to our employees.

We started to reopen the Amsterdam and Lexington facilities in phases, in line with the reopening plans that are prescribed by the local government. Between June 1, 2020 until September 29, 2020, we encouraged our Amsterdam employees to work a minimum of two days per week from the office, and approximately 50% of local staff worked on site during that period. As of September 29, 2020, we reinstated the mandatory work-from-home policy that was initiated in March in Amsterdam to align with the updated Dutch government's measures. Employees based in Amsterdam who cannot perform their duties outside of our Amsterdam facility will continue to work at our Amsterdam facility. We adapted to operate our laboratories at our Amsterdam site to comply with social distancing rules and to ensure the health and wellbeing of our employees under the current circumstances. All other employees in Amsterdam will work from home through at least the end of August 2021, partly in conjunction with the ongoing expansion of our laboratory space.

As a biopharma research and development company, we were deemed to provide essential services under the "stay at home" advisory that was issued by the Governor of Massachusetts on March 23, 2020 and we therefore have maintained our manufacturing operations at our Lexington site. To ensure adequate social distancing in our Lexington facility, our COVID-19 protocols generally have limited occupancy to numbers below those allowed by the Massachusetts COVID-19 guidelines. In our Lexington facility, we currently have implemented an occupancy limitation of approximately 25%. Our employees that cannot perform their duties outside of our Lexington facility continue to work at our Lexington facility. All other employees are required to work remotely to the extent possible through at least the end of the second quarter of 2021. Our actual occupancy at the Lexington facility has been less than approximately 25% of our permitted occupancy during all phases of the Massachusetts reopening plan. We have also implemented a mandatory COVID-19 PCR testing protocol effective February 11, 2021 that requires employees to have tested negative for COVID-19 prior to entering the Lexington facility.

We have adapted our ongoing clinical research activities based on the directions and flexibility provided by the "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" issued on March 18, 2020 and updated throughout the pandemic to minimize any risk, disruption or delay in either patient dosing or follow-up visits. These procedures occurred after a postponement that resulted from the COVID-19 pandemic and the associated states of emergency declarations in the United States.

The broader implications of COVID-19 on our results of operations and overall financial performance remain uncertain. The COVID-19 pandemic and its adverse effects have become more prevalent in the locations where we, and our third-party business partners conduct business. While we have experienced disruptions in our operations as a result of COVID-19, we are adapting to the current environment to minimize the effect to our business. However, we may experience more pronounced disruptions in our operations in the future.

Related party transaction

On December 1, 2020, we and BMS entered into the amended BMS CLA. All transactions subsequent to the effective date of the amended BMS CLA are considered to no longer be with a related party.

2020 Financial Highlights

Key components of our results of operations include the following:

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Total revenues	$ 37,514	$ 7,281	$ 11,284
Research and development expenses	(122,400)	(94,737)	(74,809)
Selling, general and administrative expenses	(42,580)	(33,544)	(25,305)
Net loss	(125,024)	(124,201)	(83,304)

As of December 31, 2020, we had cash and cash equivalents of $244.9 million (December 31, 2019: $377.8 million). We had a net loss of $125.0 million in 2020, $124.2 million in 2019 and $83.3 million in 2018. As of December 31, 2020, we had an accumulated deficit of $784.7 million (December 31, 2019: $659.7 million).

We anticipate that our expenses will increase substantially as we:

- Advance the clinical development of AMT-130 for our Huntington's disease gene therapy program;
- Build-out our commercial and medical affairs infrastructure and seek marketing approval for any product candidates (including etranacogene dezaparvovec in the event that the transactions contemplated by the CSL Behring Agreement do not close) that successfully complete clinical trials;
- Advance multiple research programs related to gene therapy candidates targeting liver-directed and CNS diseases;
- Continue to expand, enhance, and optimize our technology platform, including our manufacturing capabilities, next-generation viral vectors and promoters, and other enabling technologies;
- Acquire or in-license rights to new therapeutic targets or product candidates; and
- Maintain, expand, and protect our intellectual property portfolio, including in-licensing additional intellectual property rights from third parties.

See "Results of Operations" below for a discussion of the detailed components and analysis of the amounts above.

Critical Accounting Policies and Estimates

In preparing our consolidated financial statements in accordance with U.S. GAAP and pursuant to the rules and regulations promulgated by the SEC we make assumptions, judgments and estimates that can have a significant impact on our net income/loss and affect the reported amounts of certain assets, liabilities, revenue and expenses, and related disclosures. On an ongoing basis, we evaluate our estimates and judgments, including those related to the treatment of the CSL Behring Agreement, the amended BMS CLA, share-based payments, corporate income taxes related to valuation allowance and accounting for operating leases under ASC 842. We base our assumptions, judgments and estimates on historical experience and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not clear from other sources. Actual results may differ from these estimates under different assumptions or conditions. In making estimates and judgments, management employs critical accounting policies. We also discuss our critical accounting policies and estimates with the Audit Committee of our Board of Directors.

We believe that the assumptions, judgments, and estimates involved in the treatment of the CSL Behring Agreement, the amended BMS CLA, share-based payments, corporate income taxes related to valuation allowance and accounting for operating leases under ASC 842 to be our critical accounting policies. Historically, our assumptions, judgments and estimates relative to our critical accounting policies have not differed materially from actual results.

CSL Behring Agreement

The effectiveness of the transactions contemplated by the CSL Behring Agreement is contingent on completion of review under antitrust laws in the United States, Australia, and the United Kingdom and certain provisions of the CSL Behring Agreement will not become effective until after we receive all such regulatory approvals. We obtained regulatory approvals in Australia and the United Kingdom prior to January 6, 2021. We received a Second Request from the FTC on January 4, 2021, and as such, regulatory approval in the United States has not occurred to date. We do not believe that the FTC will determine that the consummation of the transaction will result in a violation of the HSR Act. However, there can be no assurance as to the outcome of the Second Request.

As of December 31, 2020, we concluded that we have no enforceable right to receive the $450.0 million upfront payment, in accordance with the CSL Behring Agreement as payment is contingent upon the successful completion of reviews under the HSR Act. Therefore, we determined we will not recognize any revenue in relation to the upfront payment, the regulatory and sale milestone payments, or the royalties (together "CSL Behring License Revenue") in accordance with ASC 606. We incurred $2.1 million of expenses related to obligations related to the CSL Behring Agreement that had not been satisfied as of December 31, 2020. We capitalized these expenses as we believe these qualify as contract fulfillment costs. As of December 31, 2020, we also recognized a $2.1 million receivable from CSL Behring for expenses for which we have a right of reimbursement as well as a contract liability for the same amount. In accordance with ASC 606, we cannot recognize any revenue in connection with the CSL Behring Agreement as of this date.

In accordance with our existing license and other agreements, we are contractually required to pay in total a low to high single digit percentage of any upfront payment to our licensors and financial advisor ("License Fees"). We did not record any License Fees in the year ended December 31, 2020, as we had not recognized the upfront payment as of this date.

Amended BMS CLA

In May 2015, we entered into a collaboration and license agreement and various related agreements with BMS, which we collectively refer to as the BMS CLA, which provided BMS with exclusive access to our gene therapy technology platform for the research, development and commercialization of therapeutics aimed at multiple targets in cardiovascular and other diseases. The BMS CLA provided that we and BMS could have potentially collaborated on up to ten Collaboration Targets in total. The initial four-year research term under the collaboration terminated on May 21, 2019. During the initial research term of the BMS CLA, BMS, at its option, could purchase non-clinical, analytical and process development effort services. For any Collaboration Targets that might have been advanced, BMS could have purchased clinical and commercial supplies from us. BMS reimbursed us for the services in support of the collaboration during the initial research term, and leads the development, regulatory and commercial activities for any Collaboration Targets that are advanced.

On December 1, 2020, we and BMS amended the BMS CLA. Following the amendment BMS is no longer entitled to designate a fifth to tenth Collaboration Target and as such we are no longer entitled to receive an aggregate $16.5 million in target designation payments or research, development, and regulatory milestone payments related to the fifth and tenth Collaboration Targets. For a period of one year from the effective date of the amended BMS CLA, BMS may replace up to two of the four active Collaboration Targets with two new targets in the field of cardiovascular disease. We continue to be entitled to receive up to $217.0 million for each of the four Collaboration Targets if defined milestones are achieved, as well as royalties on net sales associated with any Collaboration Target.

We evaluated the impact of the amendment of the BMS CLA in relation to our performance obligation related to:

- providing access to our technology and know-how in the field of gene therapy and participating in joint steering committee and other governing bodies (materially satisfied as of December 1, 2020) ("License Revenue").

We did not identify any new distinct performance obligations and determined the amended BMS CLA did not represent a separate contract in accordance with ASC 606. We evaluated the effect the modification has on our measure of progress towards the completion of our performance obligation in relation to License Revenue and recorded an adjustment to License Revenue as of December 1, 2020. The estimation of total services at the end of each reporting period involves considerable judgement.

The amount of services we expect to provide is significantly impacted by the number of Collaboration Targets that we estimate BMS would pursue. We considered that BMS may no longer designate potentially up to six Collaboration Targets in addition to the currently four active targets. We evaluated our obligations with respect to the two replacement cardiovascular indications that BMS might potentially designate until November 30, 2021, and the services we expected to perform in relation to participating in joint steering committee and other governing bodies as well as the effort required to actively contribute to the target selection process or the collaboration as a whole. Based on this we concluded that our remaining performance obligation is immaterial and adjusted our measure of progress accordingly. As such we recognized the remaining balance of unrecognized License Revenue as of November 30, 2020 of $27.8 million in profit and loss during the year ended December 31, 2020 as License Revenue from a related party.

In 2015 we granted BMS two warrants, which were terminated in connection with the amendment to the BMS CLA. We granted to BMS:

- A warrant that allowed BMS to purchase a specific number of our ordinary shares such that its ownership would have equaled 14.9% immediately after such purchase (1st warrant"). The 1st warrant could have been exercised on the later of (i) the date on which we received from BMS the Target Designation Fees (as defined in the BMS CLA) associated with the first six new targets (a total of seven Collaboration Targets); and (ii) the date on which BMS designated the sixth new target (the seventh Collaboration Target).
- A warrant that allowed BMS to purchase a specific number of our ordinary shares such that its ownership would have equaled 19.9% immediately after such purchase ("2nd warrant" and together with the 1st warrant, the "warrants"). The warrant could have been exercised on the later of (i) the date on which we received from BMS the Target Designation Fees associated with the first nine new targets (a total of ten Collaboration Targets); and (ii) the date on which BMS designated the ninth new target (the tenth Collaboration Target).

Pursuant to the terms of the BMS CLA the exercise price in respect of each warrant was equal to the greater of (i) the product of (A) $33.84, multiplied by (B) a compounded annual growth rate of 10% (or approximately $57.32 as of November 30, 2020) and (ii) the product of (A) 1.10 multiplied by (B) the volume weighted average price ("VWAP") for the 20 trading days ending on the date that is five trading days prior to the date of a notice of exercise delivered by BMS.

We used Monte-Carlo simulations to determine the fair market value of the BMS warrants. The valuation model incorporated several inputs, the risk-free rate adjusted for the period affected, an expected volatility based on our historical volatility, the expected yield on any dividends and management's expectations on the timelines of reaching certain defined trigger events for the exercising of the warrants, as well as management's expectations regarding the number of ordinary shares that would be issued upon exercise of the warrants. All of these represent Level 3 inputs. Additionally, the model assumed BMS would exercise the warrants only if it were financially rational to do so. The warrants could only have been exercised following the occurrence of events contractually defined in the warrant agreements. The probability of the occurrence of these events represented another significant unobservable input used in the calculation of the fair value of the warrants. The fair value of the warrants as of December 31, 2019 was $3.1 million. During the year ended December 31, 2020, we recognized a $3.1 million gain in non-operating income / expense (December 31, 2019: $2.3 million loss; December 31, 2018: $0.5 million gain) related to fair value changes of the BMS warrants. The gain recognized in the year ended December 31, 2020 includes $0.8 million from the derecognition of the BMS warrants on December 1, 2020.

On December 1, 2020, we and BMS terminated the BMS warrants and agreed that upon the consummation of a change of control transaction of uniQure that occurs prior to the earlier of (i) December 1, 2026 and (ii) BMS' delivery of a target cessation notice for all four Collaboration Targets, uniQure (or its third party acquirer) shall pay to BMS a one-time, non-refundable, non-creditable cash payment of $70.0 million, provided that (x) if $70.0 million is greater than five percent (5.0%) of the net proceeds (as contractually defined) from such change of control transaction, the payment shall be an amount equal to five percent of such net proceeds, and (y) if $70.0 million is less than one percent of such net proceeds, the change of control payment shall be an amount equal to one percent of such net proceeds ("CoC-payment"). We have not consummated any change of control transaction as of December 31, 2020 that would obligate us to make a CoC-payment. We determined that the CoC-payment should be recorded as a derivative financial liability as of December 1, 2020 and that subsequent changes in the fair market value of this derivative financial liability should be recorded in profit and loss. The fair market value of the derivative financial liability is materially impacted by probability that market participants assign to the likelihood of the occurrence of a change of control transaction that would give rise to a CoC-payment. This probability represents an unobservable input. We determined the fair market value of the derivative financial liability by using a present value model based on expected cash flow. The expected cash flows are materially impacted by the probability that market participants assign to the likelihood of the occurrence of a change of control event within the biotechnology industry. We estimated this unobservable input using the best information available as of December 1, 2020 and December 31, 2020. We obtained reasonably available market information that we believe market participants would use in determining the likelihood of the occurrence of a change-of control transaction within the biotechnology industry. Selecting and evaluating market information involves considerable judgement and uncertainty. Based on all such information and our judgment we estimated that the fair market value of the derivative financial liability (presented within "Other non-current liabilities") as of December 1, 2020 and December 31, 2020 was $2.6 million. We recorded a $2.6 million loss within "other non-operating expenses" in the twelve-month period ended December 31, 2020 related to the initial recognition of this derivative financial liability.

Share-based payments

We issue share-based compensation awards, in the form of options to purchase ordinary shares, restricted share units and performance share units, to certain of our employees, executive and non-executive board members, and consultants. We measure share-based compensation expense related to these awards by reference to the estimated fair value of the award at the date of grant. The awards are subject to service and/or performance-based vesting conditions. The total amount of the awards is expensed on a straight-line basis over the requisite vesting period.

We use a Hull & White option model to determine the fair value of option awards. The model captures early exercises by assuming that the likelihood of exercise will increase when the share-price reaches defined multiples of the strike price. This analysis is made over the full contractual term.

At each balance sheet date, we revise our estimate of the number of options that are expected to become exercisable. We recognize the impact of the revision of original estimates, if any, in the statements of operations and comprehensive loss and a corresponding adjustment to equity. We expect all vested options to be exercised over the remainder of their contractual life. We consider the expected life of the options to be in line with the average remaining term of the options post vesting.

We account for share options as an expense in the statements of operations and comprehensive loss over the estimated vesting period, with a corresponding contribution to equity, as they are all equity-classified.

Corporate income taxes

We are subject to corporate taxes in the Netherlands and the United States of America. Significant judgment is required in determining the valuation allowance in relation to our net operating loss carry forwards. We have been incurring net operating losses in accordance with the respective corporate tax laws in almost all years since we founded our business. As of December 31, 2020, the total amount of net operating losses carried forward under the Dutch tax regime was $588.2 million and $42.3 million in the United States of America.

We reassessed the need for a full valuation allowance in conjunction with entering into the CSL Behring Agreement. The effectiveness of the transactions contemplated by the CSL Behring Agreement is contingent on completion of review under antitrust laws in the United States, Australia, and the United Kingdom. Regulatory approval in the United States has not occurred to date. We recognize deferred tax assets to the extent that we determine that these assets are more likely than not to be realized. In making such a determination, we weighed all available positive and negative evidence, including future income projections from the CSL Behring Agreement, and concluded that it is more likely than not that the deferred tax assets will not be realized. Accordingly, we continued to record a full valuation allowance as of December 31, 2020 in the Netherlands. As of December 31, 2020, our valuation allowance amounted to $150.1 million (2019: $109.9 million).

We recorded $16.4 million of deferred tax income in the year ended December 31, 2020 from releasing the full valuation allowance against our net deferred tax assets in the United States as of December 31, 2020. Our U.S. entity has generated taxable income in the fiscal years 2018, 2019 and 2020. Based on the current design of our worldwide operations, we expect to continue to generate taxable income in the U.S. during the foreseeable future and therefore determined that it is more likely than not that our U.S. deferred tax assets will be realized. Our U.S. deferred tax assets as of December 31, 2020 amount to $16.4 million.

Leases

On January 1, 2019, we adopted ASC 842, “Leases (Topic 842)”. We adopted the standard using the modified retrospective approach with an effective date as of the beginning of our fiscal year, January 1, 2019, to operating leases that existed on that date. Comparative financial information related to profit and loss and cash flows for the twelve-month period ended December 31, 2018, was not recast under the new standard, and continues to be presented under ASC 840.

We measured the lease liability at the present value of the future lease payments as of January 1, 2019. We used an incremental borrowing rate to discount the lease payments. We derived the discount rate, adjusted for differences such as in the term and payment patterns, from our loan from Hercules Capital, which was refinanced immediately prior to the January 1, 2019 adoption date in December 2018. We valued the right-of-use asset at the amount of the lease liability reduced by the remaining December 31, 2018 balance of lease incentives received. The lease liability is subsequently measured at the present value of the future lease payments as of the reporting date with a corresponding adjustment to the right-to-use asset. Absent a lease modification, we will continue to utilize the January 1, 2019, incremental borrowing rate.

We recognize lease cost on a straight-line basis and present these costs as operating expenses within our Consolidated statements of operations and comprehensive loss. We present lease payments and landlord incentive payments within cash flows from operations within our Consolidated statements of cash flows.

Recent Accounting Pronouncements

ASU 2018-13: Fair Value Measurement

In August 2018, the FASB issued ASU 2018-13, Fair Value Measurement (Topic 820) which modifies the disclosure requirements on fair value measurements. The effective date for the standard is fiscal years beginning after December 15, 2019, which for us is January 1, 2020. Early adoption is permitted. The new disclosure requirements for changes in unrealized gains and losses in other comprehensive income for recurring Level 3 measurements, the range and weighted average of significant unobservable inputs and the amended requirements for the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively. ASU 2018-13 did not have a material impact on our consolidated financial statements.

Recent Accounting Pronouncements Not Yet Effective

None.

Results of Operations

The following table presents a comparison of the twelve months ended December 31, 2020, 2019 and 2018.

	Year ended December 31,				
	2020	2019	2018	2020 vs 2019	2019 vs 2018
	(in thousands)				
Total revenues	$ 37,514	$ 7,281	$ 11,284	$ 30,233	$ (4,003)
Operating expenses:					
Research and development expenses	(122,400)	(94,737)	(74,809)	(27,663)	(19,928)
Selling, general and administrative expenses	(42,580)	(33,544)	(25,305)	(9,036)	(8,239)
Total operating expenses	**(164,980)**	**(128,281)**	**(100,114)**	**(36,699)**	**(28,167)**
Other income	3,342	1,888	2,146	1,454	(258)
Other expense	(1,302)	(2,028)	(1,548)	726	(480)
Loss from operations	**(125,426)**	**(121,140)**	**(88,232)**	**(4,286)**	**(32,908)**
Non-operating items, net	(16,017)	(3,061)	5,159	(12,956)	(8,220)
Loss before income tax income / (expense)	$ **(141,443)**	$ **(124,201)**	$ **(83,073)**	**(17,242)**	**(41,128)**
Income tax income / (expense)	16,419	—	(231)	16,419	231
Net loss	**$ (125,024)**	**$ (124,201)**	**$ (83,304)**	**$ (823)**	**$ (40,897)**

Revenue

We recognize collaboration revenues associated with Collaboration Target-specific pre-clinical analytical development and process development activities that are reimbursable by BMS under the BMS CLA and the amended BMLS CLA as well as other related agreements. Collaboration Revenue related to these contracted services is recognized when performance obligations are satisfied.

We recognized license revenues associated with the amortization of the non-refundable upfront payment and target designation fees we received from BMS in 2015. We evaluated our outstanding performance obligation following the amendment of the BMS CLA on December 1, 2020 and determined that our remaining performance obligation is immaterial. We updated our measure of progress accordingly and amortized the remaining balance of unrecognized revenue as of December 1, 2020. In accordance with the amended BMS CLA, we continue to be eligible to receive research, development, and regulatory milestone payments as well as sales milestone payments and royalties for each of the four active Collaboration Targets if defined milestones are achieved in relation to the license to our technology and know-how. We will recognize revenue from these payments when earned or as sales occur.

Our revenue for the years ended December 31, 2020, 2019 and 2018 was as follows:

	Year ended December 31,				
	2020	2019	2018	2020 vs 2019	2019 vs 2018
	(in thousands)				
License revenue	$ 37,319	$ 4,988	$ 7,528	$ 32,331	$ (2,540)
Collaboration revenue	195	2,293	3,756	(2,098)	(1,463)
Total revenues	**$ 37,514**	**$ 7,281**	**$ 11,284**	**$ 30,233**	**$ (4,003)**

We recognized $37.3 million, $5.0 million, and $7.5 million of license revenue for the year ended December 31, 2020, 2019 and 2018, respectively. The increase in license revenue in 2020 of $32.2 million compared to 2019 primarily resulted from $27.8 million of license revenue that we recognized as of the December 1, 2020 effective date of the amended BMS CLA as well as $4.4 million research milestone payment that we recorded in December 2020 following the designation of one of the four Collaboration Targets as a candidate to advance into IND-enabling studies. The decrease in license revenue in 2019 of $2.5 million compared to 2018 resulted from the termination of the S100A1 Collaboration Target and subsequent designation of a replacement target in 2019.

We recognized $0.2 million, $2.3 million, and $3.8 million of collaboration revenue for the years ended December 31, 2020, 2019 and 2018, respectively. The decrease in collaboration revenue in 2020 of $2.1 million compared to 2019 was primarily related to the reduction of activities following the termination of the initial research term under the BMS CLA in May 2019. The decrease in collaboration revenue in 2019 of $1.5 million compared to 2018 resulted from the termination of the initial research term in May 2019 as well as the discontinuation of the S100A1 program in October 2018.

Research and development expenses

We expense research and development costs ("R&D") as incurred. Our R&D expenses generally consist of costs incurred for the development of our target candidates, which include:

- Employee-related expenses, including salaries, benefits, travel, and share-based compensation expense;
- Costs incurred for laboratory research, preclinical and nonclinical studies, clinical trials, statistical analysis and report writing, and regulatory compliance costs incurred with clinical research organizations and other third-party vendors;
- Costs incurred to conduct consistency and comparability studies;
- Costs incurred for the validation of our Lexington facility;
- Costs incurred for the development and improvement of our manufacturing processes and methods;
- Costs associated with our research activities for our next-generation vector and promoter platform;
- Changes in the fair value of the contingent consideration related to our acquisition of InoCard (up to September 30, 2018) as well as the impairment of in process research and development acquired in the three-month period ended September 30, 2018;
- Facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other supplies; and

Our research and development expenses primarily consist of costs incurred for the research and development of our product candidates, which include:

- *Etranacogene dezaparvovec (hemophilia B)*. We have incurred costs related to the research, development, and production of etranacogene dezaparvovec for the treatment of hemophilia B. In June 2018, we initiated a pivotal study. We completed enrollment of the lead-in phase of the pivotal study in September 2019 and dosed a total of 54 patients between January 2019 and March 2020. Following the completion of dosing we initiated activities related to the preparation of marketing authorization applications in the U.S. and EU, as well as other related undertakings. In September 2018, we completed patient dosing in our Phase IIb dose-confirmation study;
- *AMT-130 (Huntington's disease)*. We have incurred costs related to preclinical and nonclinical studies of AMT-130 and have been incurring costs related to our Phase I/II trial since February 2019;
- *Preclinical research programs*. We incur costs related to the research of multiple preclinical gene therapy product candidates with the potential to treat certain rare and other serious medical conditions; and
- *Technology platform development and other related research*. We incur significant research and development costs related to manufacturing and other enabling technologies that are applicable across all our programs.

Our research and development expenses may vary substantially from period to period based on the timing of our research and development activities, including manufacturing campaigns, regulatory submissions, and enrollment of patients in clinical trials. The successful development of our product candidates is highly uncertain. Estimating the nature, timing, or cost of the development of any of our product candidates involves considerable judgement due to numerous risks and uncertainties associated with developing gene therapies, including the uncertainty of:

- the scope, rate of progress and expense of our research and development activities;
- our ability to successfully manufacture and scale-up production;
- clinical trial protocols, speed of enrollment and resulting data;
- the effectiveness and safety of our product candidates;
- the timing of regulatory approvals; and
- our ability to agree to ongoing development budgets with collaborators who share the costs of our development programs.

A change in the outcome of any of these variables with respect to our product candidates that we may develop, including as a result of the COVID-19 pandemic, could mean a significant change in the expenses and timing associated with the development of such product candidate.

Research and development expenses for the year ended December 31, 2020 were $122.4 million, compared to $94.7 million and $74.8 million for the years ended December 31, 2019 and 2018, respectively. Other research and development expenses are separately classified in the table below. These are not allocated as they are deployed across multiple projects under development.

	Year ended December 31,				
	2020	2019	2018	2020 vs 2019	2019 vs 2018
	(in thousands)				
Etranacogene dezaparvovec (AMT-060/061)	$ 21,458	$ 16,853	$ 8,677	$ 4,605	$ 8,176
Huntington's disease (AMT-130)	6,905	4,126	5,862	2,779	(1,736)
Programs in preclinical development and platform related expenses	6,518	5,710	2,491	808	3,219
Total direct research and development expenses	**$ 34,881**	**$ 26,689**	**$ 17,030**	**$ 8,192**	**$ 9,659**
Employee and contractor-related expenses	41,694	34,030	28,948	7,664	5,082
Share-based compensation expense	11,995	8,094	3,968	3,901	4,126
Facility expenses	17,390	15,181	12,961	2,209	2,220
Disposables	10,203	8,765	9,461	1,438	(696)
Other expenses	6,237	1,978	646	4,259	1,332
Termination benefits	—	—	96	—	(96)
Changes in fair value of contingent consideration	—	—	(3,800)	—	3,800
Impairment loss in process research and development asset	—	—	5,499	—	(5,499)
Total other research and development expenses	**$ 87,519**	**$ 68,048**	**$ 57,779**	**$ 19,471**	**$ 10,269**
Total research and development expenses	**$ 122,400**	**$ 94,737**	**$ 74,809**	**$ 27,663**	**$ 19,928**

Direct research and development expenses

Hemophilia B (AMT-060/061)

In the year ended December 31, 2020, the external costs for our hemophilia B program were primarily related to the execution of our Phase III clinical trial and the preparations related to submissions of marketing authorization applications in the U.S. and EU. We enrolled patients into a six-month lead in phase between January 2018 and September 2019 and dosed a total of 54 patients between January 2019 and March 2020. Our expenses related to etranacogene dezaparvovec were largely unaffected by the COVID-19 pandemic as we completed enrollment prior to the lockdowns in those countries that we enroll patients. We implemented additional measures to minimize any risk, disruption, or delay on follow-up visits, and as of September 2020, we completed almost all follow-up visits according to our initial plan.

In addition, we continue to incur costs for the long-term follow-up of patients in our Phase I/II clinical trial of AMT-060 and our Phase IIb clinical trial of etranacogene dezaparvovec. Our Phase IIb dose-confirmation study was initiated in January 2018 and dosing occurred in July and August 2018. Patients were dosed as part of our Phase I/II clinical trial of AMT-060 in 2015 and 2016. In the years ended December 31, 2018 and 2019, our external costs for our hemophilia B program were primarily related to the planning and execution of our Phase III and Phase IIb clinical trials.

Following the completion of patient enrollment into our HOPE-B trial we also started incurring costs related to preparation of a BLA and MAA and for commercialization of etranacogene dezaparvovec.

Huntington disease (AMT-130)

In the year ended December 31, 2020, our external costs for the development of Huntington's disease were primarily related to the execution of our Phase I/II clinical trial as well as expenses related to the procedures of the first two patients in June 2020. In the year ended December 31, 2019, our external costs for the development of Huntington's disease were primarily related to the preparation of our Phase I/II clinical trial. During 2018, the majority of costs were related to the planning and execution of a GLP toxicology study. In addition, we incurred cost related to the filing of our IND in late 2018 and early 2019.

Preclinical programs & platform development

In the year ended December 31, 2020, we incurred $6.5 million of costs related to related to our preclinical activities for product candidates including Hemophilia A (AMT-180), SCA3 (AMT-150) and Fabry disease (AMT-190), as well as various other research programs and technology innovation projects compared to $5.7 million in 2019 and $2.5 million in 2018.

Other research & development expenses

- We incurred $41.7 million in employee and contractor expenses in the year ended December 31, 2020 compared to $34.0 million in 2019 and $28.9 million in 2018. Our cost increased in 2020 by $7.7 million compared to 2019 as a result of the recruitment of personnel to support the preclinical and clinical development of our product candidates. For the same reason our costs increased by $5.1 million in 2019 compared to 2018;
- We incurred $12.0 million in share-based compensation expenses in the year ended December 31, 2020 compared to $8.1 million in 2019 and $4.0 million in 2018. The increase in 2020 compared to 2019 of $3.9 million was primarily driven by grants to newly recruited personnel as well as share-based compensation expenses recorded in relation to the termination of one of our executives. The increase in 2019 compared to 2018 of $4.1 million was driven primarily by the appreciation of our share price and increase in number of grants;
- We incurred $17.4 million in operating expenses and depreciation expenses related to our rented facilities in the year ended December 31, 2020 compared to $15.2 million in 2019 and $13.0 million in 2018. The increase in 2020 compared to 2019 of $2.2 million primarily relates to extending and expanding (as of June 2019) the lease of our Lexington facility. The increase in 2019 compared to 2018 of $2.2 million also primarily relates to extending and expanding (as of June 2019) the lease of our Lexington facility;
- We incurred $10.2 million in costs in the year ended December 31, 2020 compared to $8.8 million in the year ended December 31, 2019 and $9.5 million in the year ended December 31, 2018 related to miscellaneous other costs we incur as a result of expanding our organization;
- We incurred $6.2 million in other expenses in the year ended December 31, 2020 compared to $2.0 million in 2019 and $0.6 million in 2018. The increase in 2020 compared to 2019 of $4.2 million primarily relates to license payments of $3.4 million that we determined during 2020 to have no alternative future use. The increase in 2019 compared to 2018 of $1.4 million primarily relates to extending and expanding (as of June 2019) the lease of our Lexington facility;
- We recorded no results related to a change in the fair value of the contingent consideration owed to the sellers of the InoCard business in the years ended December 31, 2020 and 2019 compared to a gain of $3.8 million in 2018; and
- We incurred no impairment losses in the years ended December 31, 2020 and 2019 compared to an impairment loss of $5.4 million on the in-process research and development asset acquired in the InoCard business combination in 2018.

Selling, general and administrative expenses

Our general and administrative expenses consist principally of employee, office, consulting, legal and other professional and administrative expenses. We incur expenses associated with operating as a public company, including expenses for personnel, legal, accounting and audit fees, board of directors' costs, directors' and officers' liability insurance premiums, Nasdaq listing fees, expenses related to investor relations and fees related to business development and maintaining our patent and license portfolio. Our selling costs include employee expenses as well as professional fees related to the preparation of a commercial launch of etranacogene dezaparvovec.

Selling, general and administrative expenses for the year ended December 31, 2020 were $42.6 million, compared to $33.5 million and $25.3 million for the years ended December 31, 2019 and 2018, respectively.

- We incurred $13.6 million in personnel and consulting expenses in 2020 compared to $10.5 million in 2019 and $8.9 million in 2018. The increase of $3.1 million in 2020 compared to 2019 and the increase of $1.6 million in 2019 compared to 2018 was primarily driven by an increase in personnel and consulting related expenses to support our growth;
- We incurred $9.8 million of share-based compensation expenses in 2020 compared to $9.4 million in 2019 and $6.7 million in 2018. The increase in 2020 compared to 2019 of $0.4 million was primarily driven by newly recruited personnel and the increase in 2019 compared to 2018 of $2.7 million was primarily driven by the appreciation of our share price and increase in number of grants;
- We incurred $8.0 million in professional fees in 2020 compared to $6.0 million in 2019 and $4.2 million in 2018. We regularly incur accounting, audit and legal fees associated with operating as a public company. Additionally, in the year ended December 31, 2020, we incurred professional fees in relation to our licensing transaction with CSL Behring.

Other items, net

In 2020, we recognized $1.9 million in income related to payments received from European authorities to subsidize our research and development efforts in the Netherlands compared to $0.7 million in 2019 and $1.0 million in 2018.

In January 2018, we began recognizing other income from the subleasing of a portion of our Amsterdam facility. We present expenses related to such income as other expense.

Other non-operating items, net

We recognize interest income associated with our cash and cash equivalents.

We hold monetary items and enter into transactions in foreign currencies, predominantly in euros and U.S. dollars. We recognize foreign exchange results related to changes in these foreign currencies.

We issued warrants to Hercules in 2013 and to BMS in 2015. We recognize changes in the fair value of these warrants within other non-operating income / (expense). Following the termination of the BMS warrants on December 1, 2020, we no longer recognize changes in the fair value of these warrants within other non-operating (expense) / income. As of the same date, we recognized a derivative financial liability related to the CoC-payment. Following the exercise of the warrants by Hercules in February 2019 we no longer recognize changes in the fair value of these warrants within other non-operating (expense) / income.

Our non-operating items, net, for the years ended December 31, 2020, 2019 and 2018 were as follows:

	Year ended December 31,				
	2020	2019	2018	2020 vs 2019	2019 vs 2018
	(in thousands)				
Interest income	$ 938	$ 3,547	$ 2,729	$ (2,609)	$ 818
Interest expense	(3,825)	(3,810)	(2,160)	(15)	(1,650)
Foreign currency (losses) / gains, net	(13,613)	(268)	4,382	(13,345)	(4,650)
Other non-operating gains / (losses), net	483	(2,530)	208	3,013	(2,738)
Total non-operating income / (loss), net	**$ (16,017)**	**$ (3,061)**	**$ 5,159**	**$ (12,956)**	**$ (8,220)**

We recognized $0.9 million interest income in 2020, $3.5 million in 2019 and $2.7 million in 2018. Our interest income in 2020 decreased by $2.6 million compared to 2019 due to a reduction in market interest rates in 2020 as well as a reduction in cash and cash equivalents. Our interest income in 2019 increased by $0.8 million as a result of an increase in our cash and cash equivalents through our September 2019 $242.7 million public follow-on offering.

We recognized $3.8 million interest expense in 2020, $3.8 million in 2019 and $2.2 million in 2018. Our interest income in 2020 was unchanged compared to 2019 as our outstanding debt remained unchanged. Our interest expense in 2019 increased by $1.6 million as we increased our outstanding debt from $20.0 million to $35.0 million on December 6, 2018.

In 2020, we recognized a net foreign currency loss of $13.6 million related to our borrowings from Hercules and our cash and cash equivalents as well as loans between entities within the uniQure group, compared to a net loss of $0.3 million in 2019 and a net gain of $4.4 million in 2018.

In 2020, we recognized a $0.5 million net gain related to fair value changes of derivative financial instruments, compared to a net loss of $2.5 million in 2019 and a gain of $0.2 million in 2018. The changes in 2020 compared to 2019 result from a $3.1 million gain that we recognized related to fair value changes of the BMS warrants (compared to $2.5 million loss in 2019), which includes an $0.8 million gain that we recognized related to the termination of the BMS warrants in December 2020, and a loss of $2.6 million to recognize the derivative financial liability for the CoC-payment on December 1, 2020.

Income tax

We recognized $16.4 million of deferred tax income in 2020, $0.0 million in 2019 and income tax expense of $0.2 million in 2018. Deferred tax income recorded in 2020 results from the release of the valuation allowance recorded for our net deferred tax assets by our U.S. entity. We did not record changes in valuation allowances in 2019 and 2018.

Financial Position, Liquidity and Capital Resources

As of December 31, 2020, we had cash, cash equivalents and restricted cash of $247.7 million. We believe our cash and cash equivalents as of December 31, 2020, combined with the $100.0 million 2021 Amended Facility will enable us to fund our operating expenses, including our debt repayment obligations, as they become due and capital expenditure requirements into the second half of 2022. In the event that we receive the $450.0 million payment due on the closing of the CSL Behring Agreement, we expect that our cash and cash equivalents will be sufficient to fund operations into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules under our term loan facility by 2023). The table below summarizes our consolidated cash flow data for the years ended December 31:

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Cash, cash equivalents and restricted cash at the beginning of the period	$ 380,726	$ 237,342	$ 161,851
Net cash used in operating activities	(134,828)	(98,684)	(76,037)
Net cash used in investing activities	(9,484)	(6,647)	(4,245)
Net cash generated from financing activities	7,444	248,821	157,961
Foreign exchange impact	3,822	(106)	(2,187)
Cash, cash equivalents and restricted cash at the end of period	**$ 247,680**	$ 380,726	$ 237,342

We have incurred losses and cumulative negative cash flows from operations since our business was founded by our predecessor entity AMT in 1998. We had a net loss of $125.0 million in 2020, $124.2 million in 2019, and $83.3 million in 2018. As of December 31, 2020, we had an accumulated deficit of $784.7 million.

Sources of liquidity

From our first institutional venture capital financing in 2006 through 2019, we funded our operations primarily through private placements and public offerings of equity securities, convertible, and other debt securities and to a lesser extent upfront, target designation or similar payments from our collaboration partners.

On September 10, 2019, we completed a follow-on public offering of 4,891,305 ordinary shares at a public offering price of $46.00 per ordinary share, and on September 13, 2019, we completed the sale of an additional 733,695 ordinary shares at a public offering price of $46.00 per ordinary share pursuant to the exercise by the underwriters of the option to purchase additional ordinary shares, resulting in total gross proceeds to us of $258.8 million. The net proceeds from this offering were $242.7 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. We deducted $0.6 million of expenses incurred related to this offering from additional paid-in capital in the accompanying consolidated balance sheets and reflected this within the proceeds from public offering of shares, net of issuance costs within the cash flows from financing activities.

On December 6, 2018, we signed an amendment to the Second Amended and Restated Loan and Security Agreement (the "2018 Amended Facility") with Hercules that both refinanced our then-existing $20.0 million credit facility and provided us with an additional unconditional commitment of $15.0 million as well as a conditional commitment of $15.0 million that expired on June 30, 2020. At signing, we drew down an additional $15.0 million, for a total outstanding amount of $35.0 million.

The 2018 Amended Facility extended the loan's maturity date until June 1, 2023. The interest-only period was initially extended from November 2018 to January 1, 2021. The interest-only period was further extended to January 1, 2022 as a result of raising more than $90.0 million in equity financing in September 2019. As of December 31, 2020, $35.0 million was outstanding under the 2018 Amended Facility (December 31, 2019: $35.0 million). We are required to repay the facility in equal monthly installments of principal and interest between the end of the interest-only period and the maturity date. The variable interest rate is equal to the greater of (i) 8.85% or (ii) 8.85% plus the prime rate less 5.50%. Under the 2018 Amended Facility, we paid a facility fee equal to 0.50% of the $35,000,000 loan outstanding and will owe a back-end fee of 4.95% of the outstanding debt.

On January 29, 2021 we and Hercules entered into the 2021 Amended Facility. Pursuant to the 2021 Amended Facility, Hercules agreed to the 2021 Term Loan, increasing the aggregate principal amount of the term loan facility from $35.0 million to up to $135.0 million. On January 29, 2021 we drew down $35.0 million of the 2021 Term Loan. We may draw down the remaining $65.0 million under the 2021 Term Loan in a series of one or more advances of not less than $20.0 million each until December 15, 2021. Advances under the 2021 Term Loan bear interest at a rate equal to the greater of (i) 8.25% or (ii) 8.25% plus the prime rate, less 3.25% per annum. The principal balance and all accrued but unpaid interest on advances under the 2021 Term Loan is due on June 1, 2023, which date may be extended by us by up to two twelve-month periods. Advances under the 2021 Term Loan may not be prepaid until six-months after the Closing Date, following which we may prepay all such advances without charge.

On May 7, 2018, we completed a follow-on public offering of 5,175,000 ordinary shares at a public offering price of $28.50 per ordinary share, resulting in gross proceeds to us of $147.5 million. The net proceeds from this offering were $138.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. We deducted $0.2 million of expenses incurred related to this offering from additional paid-in capital in the accompanying consolidated balance sheet and reflected this within the proceeds from public offering of shares, net of issuance costs with the cash flows from financing activities.

The $450.0 million upfront payment we expect to receive on the closing of the CSL Behring Agreement would fund operations into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules under our term loan facility by 2023). The closing of the transaction is expected to materially impact our profitability and cash flows. We expect to generate positive cash flows in the period of closing and to recognize material revenue related to the CSL Behring Agreement. However, we expect to continue to incur losses and to generate negative cash flows beyond the fiscal year in which we close the transaction. Until such time, if ever, as we can generate substantial cash flows from successfully commercializing our proprietary product candidates, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution, and licensing arrangements.

We are subject to the same covenants under our 2018 Amended Facility and 2021 Amended Facility and may become subject to covenants under any future indebtedness that could limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, or declaring dividends, which could adversely impact our ability to conduct our business. In addition, our pledge of assets as collateral to secure our obligations under the 2018 Amended Facility and 2021 Amended Facility may limit our ability to obtain debt financing. To the extent we need to finance our cash needs through equity offerings or debt financings, such financing may be subject to unfavorable terms including without limitation, the negotiation and execution of definitive documentation, as well as credit and debt market conditions, and we may not be able to obtain such financing on terms acceptable to us or at all. If financing is not available when needed, including through debt or equity financings, or is available only on unfavorable terms, we may be unable to meet our cash needs. If we raise additional funds through collaborations, strategic alliances or marketing, distribution, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves, which could have a material adverse effect on our business, financial conditions, results of operations and cash flows.

Net Cash used in operating activities

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Cash flows from operating activities			
Net loss	$ (125,024)	$ (124,201)	$ (83,304)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation, amortization, and impairment losses	10,648	6,669	12,415
Share-based compensation expense	21,831	17,533	10,708
Change in fair value of derivative financial instruments and contingent consideration	(483)	2,530	(4,054)
Unrealized foreign exchange losses / (gains)	14,730	891	(5,502)
Deferred tax (income) / expense	(16,419)	-	231
Change in lease incentives	-	-	(330)
Change in deferred revenue	(33,642)	(4,999)	(8,462)
Changes in operating assets and liabilities:			
Accounts receivable and accrued income, prepaid expenses, and other current assets	(6,967)	(4,769)	1,578
Accounts payable	(2,701)	1,652	1,065
Accrued expenses, other liabilities, and operating leases	3,199	6,010	(382)
Net cash used in operating activities	**$ (134,828)**	**$ (98,684)**	**$ (76,037)**

Net cash used in operating activities was $134.8 million for the annual period ended December 31, 2020, and consisted of a net loss of $125.0 million adjusted for non-cash items, including depreciation and amortization expense of $10.6 million, share-based compensation expense of $21.8 million, fair value gain of derivative financial instruments of $0.5 million, unrealized foreign exchange loss of $14.7 million, a change in deferred tax income of $16.4 million and a decrease in unamortized deferred revenue of $33.6 million. Net cash used in operating activities also included unfavorable changes in operating assets and liabilities of $6.5 million. These changes primarily related to a net increase in accounts receivable and accrued income, prepaid expenses, and other current assets of $7.0 million and a net increase in accounts payable, accrued expenses, other liabilities, and operating leases of $0.5 million.

Net cash used in operating activities was $98.7 million for the annual period ended December 31, 2019, and consisted of a net loss of $124.2 million adjusted for non-cash items, including depreciation and amortization expense of $6.7 million, share-based compensation expense of $17.5 million, fair value loss of derivative financial instruments of $2.5 million, unrealized foreign exchange loss of $0.9 million, and a decrease in unamortized deferred revenue of $5.0 million. Net cash used in operating activities also included changes in operating assets and liabilities of $2.9 million. These changes primarily related to a net increase in accounts receivable and accrued income, prepaid expenses, and other current assets of $4.8 million and a net increase in accounts payable, accrued expenses, other liabilities, and operating leases of $7.7 million primarily related to our clinical trials and facilities.

Net cash used in operating activities was $76.0 million for the annual period ended December 31, 2018, and consisted of a net loss of $83.3 million adjusted for non-cash items, including depreciation and amortization expense of $12.4 million, share-based compensation expense of $10.7 million, fair value gain of derivative financial instruments and contingent consideration of $4.1 million, unrealized foreign exchange loss of $5.5 million, deferred tax of $0.2 million, an increase in lease incentives of $0.3 million, and a decrease in unamortized deferred revenue of $8.5 million. Net cash used in operating activities also included changes in operating assets and liabilities of $2.3 million net.

Net cash used in investing activities

In 2020, we used $9.5 million in our investing activities compared to $6.6 million in 2019 and $4.2 million in 2018.

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Build out of Lexington site	$ (2,737)	$ (4,164)	$ (1,596)
Build out of Amsterdam site	(4,534)	(1,487)	(788)
Acquisition of licenses, patents and other rights	(2,213)	(996)	(1,861)
Total investments	**$ (9,484)**	**$ (6,647)**	**$ (4,245)**

In 2020, we invested $2.7 million in our facility in Lexington compared to $4.2 million in 2019 and $1.6 million in 2018. Our investments in 2019 primarily relate to improvements we made to the additional space rented from June 1, 2019.

In 2020, we invested $4.5 million in our facility in Amsterdam compared to $1.5 million in 2019 and $0.8 million in 2018. Our investments in 2020 primarily relate to the construction of additional laboratories to support the expansion of our preclinical activities.

Net cash generated from financing activities

We received net proceeds of $242.7 million associated with our public follow-on offering in September 2019 and $138.4 million associated with our public follow-on offering in May 2018.

We received net proceeds of $0.5 million associated with the exercise of the Hercules warrants by Hercules in February 2019.

We received net proceeds of $14.8 million associated with the 2018 Amended Facility in December 2018.

In 2020, we received $7.4 million from the exercise of options to purchase ordinary shares issued in accordance with our share incentive plans, compared to $5.6 million in 2019 and $4.8 million in 2018.

Funding requirements

We believe our cash and cash equivalents as of December 31, 2020, combined with the $100.0 million 2021 Amended Facility, will enable us to fund our operating expenses, including our debt repayment obligations, as they become due and capital expenditure requirements into the second half of 2022. In the event that we receive the $450.0 million payment due on the closing of the CSL Behring Agreement, we expect that our cash and cash equivalents would be sufficient to fund operations into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules under our term loan facility by 2023). Our future capital requirements will depend on many factors, including but not limited to:

- the closing of the transaction contemplated by the CSL Behring Agreement as well as achieving the milestones and royalties as defined therein;
- the cost and timing of future commercialization activities, including product manufacturing, marketing, sales, and distribution of any of our product candidates for which we receive marketing approval in the future;
- the amount and timing of revenue, if any, we receive from commercial sales of any product candidates for which we, or our collaboration partner, receives marketing approval in the future;
- the scope, timing, results, and costs of our current and planned clinical trials, including those for etranacogene dezaparvovec in hemophilia B and AMT-130 in Huntington's disease;
- the scope, timing, results and costs of preclinical development and laboratory testing of our additional product candidates;
- the need for additional resources and related recruitment costs to support the preclinical and clinical development of our product candidates;
- the need for any additional tests, studies, or trials beyond those originally anticipated to confirm the safety or efficacy of our product candidates and technologies;
- the cost, timing and outcome of regulatory reviews associated with our product candidates;
- our ability to enter into collaboration arrangements in the future;
- the costs and timing of preparing, filing, expanding, acquiring, licensing, maintaining, enforcing, and prosecuting patents and patent applications, as well as defending any intellectual property-related claims;
- the repayments of the principal and other fees associated with our venture debt loan with Hercules, which following the January 29, 2021 amendment will be due in June 2023;
- the extent to which we acquire or in-license other businesses, products, product candidates or technologies;
- the costs associated with maintaining quality compliance and optimizing our manufacturing processes, including the operating costs associated with our Lexington, Massachusetts manufacturing facility;
- the costs associated with increasing the scale and capacity of our manufacturing capabilities; and
- the costs associated in preparing for the BLA submission of etranacogene dezaparvovec, including process validation, inspection readiness and other regulatory expenses in the event that our collaboration and license agreement with CSL Behring does not close.

Contractual obligations and commitments

The table below sets forth our contractual obligations and commercial commitments as of December 31, 2020, that are expected to have an impact on liquidity and cash flows in future periods. The obligations to repay debt do not reflect the extension of the interest-only period that we and Hercules agreed upon on January 29, 2021.

	Less than 1 year	Between 1 and 3 years	Between 3 and 5 years	Over 5 years	Total
			(in thousands)		
Debt obligations (including $7.4 million interest payments)	$ 3,141	$ 39,271	$ —	$ —	$ 42,412
Operating lease obligations	5,637	11,566	12,977	29,192	59,372
Total	**$ 8,778**	**$ 50,837**	**$ 12,977**	**$ 29,192**	**$ 101,784**

We have obligations to make future payments to third parties that become due and payable on the achievement of certain development, regulatory and commercial milestones (such as the start of a clinical trial, filing of a Biologics License Application, approval by the FDA or product launch). We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not fixed and determinable. We will also have obligations to make future payments that become due and payable if we collect the upfront payment or milestone payments from CSL Behring. We have not included these commitments on our balance sheet or in the table above because these payments only become due and payable upon the closing of the transaction with CSL Behring.

We enter into contracts in the normal course of business with CROs for preclinical research studies and clinical trials, research supplies and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

Off-Balance Sheet Arrangements

As of December 31, 2020, we did not have any off-balance sheet arrangement as defined in Item 303(a)(4) of Regulation S-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to a variety of financial risks in the normal course of our business, including market risk (including currency, price, and interest rate risk), credit risk and liquidity risk. Our overall risk management program focuses on preservation of capital and the unpredictability of financial markets and has sought to minimize potential adverse effects on our financial performance and position.

Market Risk

Currency risk

We are exposed to foreign exchange risk arising from various currencies, primarily with respect to the U.S. dollar and euro and to a lesser extent to the British pound. As our U.S. operating entity primarily conducts its operations in U.S. dollars, its exposure to changes in foreign currency is insignificant.

Our Dutch entities hold significant amounts of U.S. dollars in cash and cash equivalents, have debt and interest obligations to Hercules denominated in U.S. dollars, generate collaboration revenue denominated in U.S. dollars, receive services from vendors denominated in U.S. dollars and occasionally British Pounds and fund the operations of our U.S. operating entity in U.S. dollars. Foreign currency denominated account receivables and account payables are short-term in nature (generally 30 to 45 days).

Variations in exchange rates will impact earnings and other comprehensive income. On December 31, 2020, if the euro had weakened 10% against the U.S. dollar with all other variables held constant, pre-tax earnings for the year would have been $13.0 million higher (December 31, 2019: $24.7 million higher), and other comprehensive income would have been $5.2 million higher (December 31, 2019: $31.9 million lower). Conversely, if the euro had strengthened 10% against the U.S. dollar with all other variables held constant, pre-tax earnings for the year would have been $13.0 million lower (December 31, 2019: $24.7 million lower), and other comprehensive income would have been $8.3 million lower (December 31, 2019: $31.8 million higher).

We strive to mitigate foreign exchange risk through holding sufficient funds in euro and dollars to finance budgeted cash flows for the next year.

The sensitivity in other comprehensive income to fluctuations in exchange rates primarily relates to the translation of the net assets of our Dutch entities from their functional currency euro into our reporting currency U.S. dollar.

Price risk

The market prices for the provision of preclinical and clinical materials and services, as well as external contracted research, may vary over time.

The commercial prices of any of our products or product candidates are currently uncertain.

We are not exposed to commodity price risk.

We do not hold investments classified as available-for-sale or at fair value through profit or loss; therefore, we are not exposed to equity securities price risk.

Interest rate risk

Our interest rate risk arises from short- and long-term debt. In June 2013, we entered into the Hercules Agreement, which was last amended and restated in December 2018, under which our borrowings bear interest at a variable rate with a fixed floor. Long-term debt issued at fixed rates expose us to fair value interest rate risk. As of December 31, 2020, the loan bore an interest rate of 8.85%.

As of December 31, 2020, if interest rates on borrowings had been 1.0% higher with all other variables held constant, pre-tax earnings for the year would have been $0.3 million (2019: $0.3 million; 2018: $0.2 million) lower.

Credit Risk

Credit risk is managed on a consolidated basis. Credit risk arises from cash and cash equivalents and deposits with banks and financial institutions, outstanding receivables and committed transactions with collaboration partners and security deposits paid to landlords. We currently have no wholesale debtors other than BMS.

We deposited funds as security to our landlords related to our facility in Lexington, Massachusetts, and our facility in Amsterdam. We also deposited funds to the provider of our U.S. corporate credit cards. The deposits are neither impaired nor past due.

Our cash and cash equivalents include bank balances, demand deposits and other short-term highly liquid investments (with maturities of less than three months at the time of purchase) that are readily convertible into a known amount of cash and are subject to an insignificant risk of fluctuation in value. Restricted cash includes deposits made in relation to facility leases. Cash, cash equivalents and restricted cash were placed at the following banks:

	As of December 31,			
	2020		2019	
	Amount	Credit rating	Amount	Credit rating
	(in thousands)			
Bank				
Bank of America	$ 73,922	Aa2	$ 315,720	Aa2
Rabobank	173,758	Aa3	63,262	Aa3
Citizens Bank	—	-	1,744	A1
Total	**$ 247,680**		**$ 380,726**	

Ratings are by Moody's.

Liquidity Risk

We believe our cash and cash equivalents as of December 31, 2020, combined with the $100.0 million 2021 Amended Facility will enable us to fund our operating expenses, including our debt repayment obligations, as they become due and capital expenditure requirements into the second half of 2022. In the event that we receive the $450.0 million payment due on the closing of the CSL Behring Agreement, we expect that our cash and cash equivalents will be sufficient to fund operations into the second half of 2024 (assuming a full repayment of funds borrowed from Hercules under our term loan facility by 2023). We manage liquidity through a rolling forecast of our liquidity reserve based on expected cash flows and raise cash if needed, either through the issuance of shares or credit facilities.

The table below analyzes our financial liabilities in relevant maturity groupings based on the length of time until the contractual maturity date, as of the balance sheet date. Disclosed in the table below are the contractual undiscounted cash flows. Balances due within 12 months equal their carrying value as the impact of discounting is not significant.

	Undefined	Less than 1 year	Between 1 - 3 years	Between 3 - 5 years	Over 5 years
			(in thousands)		
At December 31, 2019					
Long-term debt	$ —	$ 4,119	$ 28,143	$ 14,269	$ —
Accounts payable, accrued expenses and other current liabilities	—	18,138	—	—	—
Derivative financial instruments	3,075	—	—	—	—
Total	**$ 3,075**	**$ 22,257**	**$ 28,143**	**$ 14,269**	**$ —**
At December 31, 2020					
Long-term debt	$ —	$ 3,141	$ 39,271	$ —	$ —
Accounts payable, accrued expenses and other current liabilities	—	21,810	—	—	—
Derivative financial instruments	2,645	—	—	—	—
Total	**$ 2,645**	**$ 24,951**	**$ 39,271**	**$ —**	**$ —**

Due to uncertainty of timing of exercise of warrants by BMS, the amount owed to derivative financial instruments was classified as undefined in time as of December 31, 2019. We derecognized the warrants on December 1, 2020 when these were terminated by the amended BMS CLA. On December 1, 2020 we recognized a derivative financial liability related to the CoC-payment. Generally, the CoC-payment would be due to BMS upon the consummation of a change in control transaction prior to November 30, 2026 or BMS's delivery of cessation notices for all four active Collaboration Targets. The derivative financial liability therefore has no contractual maturity date.

Item 8. Financial Statements and Supplementary Data

Our consolidated financial statements and the notes thereto, included in Part IV, Item 15, are incorporated by reference into this Item 8.

Selected quarterly financial data (unaudited)

You should read the following tables presenting our unaudited quarterly results of operations in conjunction with the consolidated financial statements and related notes contained elsewhere in this Annual Report on Form 10-K. We have prepared this unaudited information on the same basis as our audited consolidated financial statements. Our quarterly operating results have fluctuated in the past and may continue to do so in the future as a result of several factors, including, but not limited to, the timing and nature of research and development activities.

Summarized quarterly information for the two fiscal years ended December 31, 2020 and 2019, respectively, is as follows:

	For the Quarter Ended (unaudited)			
	December 31, 2020	September 30, 2020	June 30, 2020	March 31, 2020
	(in thousands, except per share data)			
Revenue	$ 34,086	$ 1,789	$ 1,535	$ 104
Net loss	(699)	(53,775)	(42,551)	(27,999)
Basic net loss per ordinary share	$ (0.02)	$ (1.21)	$ (0.96)	$ (0.63)

Note: basic net loss per ordinary share for the four quarters in 2020 does not equal the annual reported amount due to rounding.

	For the Quarter Ended (unaudited)			
	December 31, 2019	September 30, 2019	June 30, 2019	March 31, 2019
	(in thousands, except per share data)			
Revenue	$ 2,625	$ 1,046	$ 2,474	$ 1,136
Net loss	(41,426)	(23,604)	(31,399)	(27,772)
Basic net loss per ordinary share	$ (0.95)	$ (0.58)	$ (0.83)	$ (0.74)

Note: basic net loss per ordinary share for the four quarters in 2019 does not equal the annual reported amount due to rounding.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our chief executive officer ("CEO"), who also serves as our chief financial officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the "Exchange Act")) as of December 31, 2020. Based on such evaluation, our CEO has concluded that as of December 31, 2020, our disclosure controls and procedures were effective.

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 our assets that could have a material effect on the financial statements.

We assessed the effectiveness of our internal control over financial reporting as of December 31, 2020. This assessment was performed under the direction and supervision of our CEO and based on criteria established in Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO"). Our management's assessment of the effectiveness of our internal control over financial reporting included testing and evaluating the design and operating effectiveness of our internal controls. In our management's opinion, we have maintained effective internal control over financial reporting as of December 31, 2020, based on criteria established in the COSO 2013 framework.

Our independent registered public accounting firm, which has audited the consolidated financial statements included in this Annual Report on Form 10-K, has also issued an audit report on the effectiveness of our internal control over financial reporting as of December 31, 2020. Their report is filed within this Annual Report on Form 10-K.

Inherent Limitations of Internal Controls

Our management, including our CEO, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a 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 management override of the control. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements due to error or fraud.

Changes in internal control over financial reporting

During the fourth quarter of 2020, there were no changes in our internal control over financial reporting (as defined in Rule 13a-15(f) under the Exchange Act) that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting. We have not experienced any material impact to our internal controls over financial reporting even though a large group of our employees are working remotely due to the COVID-19 pandemic. We are continually monitoring and assessing the impact COVID-19 has on the operating effectiveness of our internal controls.

Item 9B. Other Information

None.

Part III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item regarding our directors, executive directors and corporate governance is incorporated into this section by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders or will be included in an amendment to this Annual Report on Form 10-K.

Item 11. Executive Compensation

The information required by this Item regarding executive compensation is incorporated into this section by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders or will be included in an amendment to this Annual Report on Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item regarding security ownership of certain beneficial owners, management and related stockholder matters, our equity compensation plans and securities under our equity compensation plans, is incorporated into this section by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders or will be included in an amendment to this Annual Report on Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item regarding certain relationships and related transactions and director independence is incorporated into this section by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders or will be included in an amendment to this Annual Report on Form 10-K.

Item 14. Principal Accounting Fees and Services

The information required by this Item regarding our principal accountant fees and services is incorporated into this section by reference to our Proxy Statement for our 2021 Annual Meeting of Shareholders or will be included in an amendment to this Annual Report on Form 10-K.

Part IV

Item 15. Exhibits, Financial Statements Schedules

Exhibits, Financial Statements Schedules

(a) *Financial Statements*. The following consolidated financial statements of uniQure N.V. are filed as part of this report:

(b) *Financial Statements Schedules*. Financial Statement Schedules have been omitted because of the absence of conditions under which they are required or because the required information, where material, is shown in the financial statements or notes.

(c) *Other Exhibits*. The Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K is incorporated herein by reference.

Item 16. Form 10-K Summary

Not applicable.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS
FOR THE YEARS ENDED DECEMBER 31, 2020, 2019 AND 2018

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
uniQure N.V.:

Opinions on the Consolidated Financial Statements and Internal Control Over Financial Reporting

We have audited the accompanying consolidated balance sheets of uniQure N.V. and subsidiaries (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, shareholders' equity, and cash flows for the years then ended, and the related notes (collectively, the consolidated financial statements). We also have audited the Company's internal control over financial reporting as of December 31, 2020, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2020 and 2019, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020 based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Change in Accounting Principle

As discussed in Note 6, to the consolidated financial statements, the Company changed its method of accounting for leases as of January 1, 2019 due to the adoption of ASC 842, *Leases*.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's consolidated financial statements and an opinion on the Company's internal control over financial reporting based on our audits. 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 audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting 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.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Assessment of the satisfaction of the license revenue performance obligation within the BMS collaboration and license agreement

As discussed in Notes 2.3.18 and 3 to the consolidated financial statements, uniQure biopharma B.V., a subsidiary of uniQure N.V. (the Company) entered into an amended collaboration and license agreement (CLA) with Bristol-Myers Squibb Company (BMS) on December 1, 2020. Based on the terms of the amended agreement, the Company determined that it materially satisfied its performance obligation in relation to the license revenue as of December 1, 2020, and as such recorded the residual balance of unrecognized license revenue of $27.8 million in profit and loss as license revenues from related party.

We identified the assessment of the satisfaction of the license revenue performance obligation as a critical audit matter. A high degree of subjective, complex auditor judgement was required in assessing if the remaining rights of the license revenue performance obligation were materially satisfied as of December 1, 2020.

The following are the primary procedures we performed to address this critical audit matter:

- We evaluated the design and tested the operating effectiveness of an internal control related to the evaluation of the performance obligation and when it was materially satisfied.

- In order to assess that the remaining rights of the license revenue performance obligation were materially satisfied, we examined the amended collaboration and license agreement between the Company and BMS.

- In order to assess the satisfaction of the performance obligation, we examined minutes of joint steering committee meetings between the Company and BMS, evaluated the services delivered and performed interviews with the Company's finance and business operations department.

/s/ KPMG Accountants N.V.

We have served as the Company's auditor since 2019.

Amstelveen, The Netherlands
March 1, 2021

Report of Independent Registered Public Accounting Firm

To the Management Board and Shareholders of uniQure N.V.:

Opinion on the Financial Statements

We have audited the consolidated statements of operations and comprehensive loss, of shareholders' equity and of cash flows of uniQure N.V. and its subsidiaries (the "Company") for the year ended December 31, 2018, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the results of operations and cash flows of the Company for the year ended December 31, 2018 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated 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 of these consolidated financial statements 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 consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ R.M.N. Admiraal RA

PricewaterhouseCoopers Accountants N.V.
Amsterdam, the Netherlands

February 28, 2019

We served as the Company's auditor from 2006 to 2019.

uniQure N.V.

CONSOLIDATED BALANCE SHEETS

	December 31, 2020	December 31, 2019
	(in thousands, except share and per share amounts)	
Current assets		
Cash and cash equivalents	$ 244,932	$ 377,793
Accounts receivables	6,618	—
Accounts receivable from related party	—	947
Prepaid expenses	4,337	4,718
Other current assets	3,024	748
Total current assets	**258,911**	**384,206**
Non-current assets		
Property, plant and equipment, net	32,328	28,771
Operating lease right-of-use assets	26,086	26,797
Intangible assets, net	3,361	5,427
Goodwill	542	496
Restricted cash	2,748	2,933
Deferred tax asset	16,419	—
Total non-current assets	**81,484**	**64,424**
Total assets	**$ 340,395**	**$ 448,630**
Current liabilities		
Accounts payable	$ 3,772	$ 5,681
Accrued expenses and other current liabilities	18,038	12,457
Current portion of operating lease liabilities	5,524	5,865
Current portion of deferred revenue	—	7,627
Total current liabilities	**27,334**	**31,630**
Non-current liabilities		
Long-term debt	35,617	36,062
Operating lease liabilities, net of current portion	30,403	31,133
Deferred revenue, net of current portion	—	23,138
Derivative financial instruments related party	—	3,075
Other non-current liabilities	3,136	534
Total non-current liabilities	**69,156**	**93,942**
Total liabilities	**96,490**	**125,572**
Commitments and contingencies		
Shareholders' equity		
Ordinary shares, €0.05 par value: 60,000,000 shares authorized at December 31, 2020 and December 31, 2019 and 44,777,799 and 43,711,954 ordinary shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	2,711	2,651
Additional paid-in-capital	1,016,018	986,803
Accumulated other comprehensive income / (loss)	9,907	(6,689)
Accumulated deficit	(784,731)	(659,707)
Total shareholders' equity	**243,905**	**323,058**
Total liabilities and shareholders' equity	**$ 340,395**	**$ 448,630**

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

uniQure N.V.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

	Year ended December 31,		
	2020	2019	2018
	(in thousands, except share and per share amounts)		
License revenues	4,352	—	—
License revenues from related party	32,967	4,988	7,528
Collaboration revenues	59	—	—
Collaboration revenues from related party	136	2,293	3,756
Total revenues	**37,514**	**7,281**	**11,284**
Operating expenses:			
Research and development expenses	(122,400)	(94,737)	(74,809)
Selling, general and administrative expenses	(42,580)	(33,544)	(25,305)
Total operating expenses	**(164,980)**	**(128,281)**	**(100,114)**
Other income	3,342	1,888	2,146
Other expense	(1,302)	(2,028)	(1,548)
Loss from operations	**(125,426)**	**(121,140)**	**(88,232)**
Interest income	938	3,547	2,729
Interest expense	(3,825)	(3,810)	(2,160)
Foreign currency (losses) / gains, net	(13,613)	(268)	4,382
Other non-operating gains / (losses), net	483	(2,530)	208
Loss before income tax income / (expense)	**$ (141,443)**	**$ (124,201)**	**$ (83,073)**
Income tax income / (expense)	16,419	—	(231)
Net loss	**$ (125,024)**	**$ (124,201)**	**$ (83,304)**
Other comprehensive income / (loss):			
Foreign currency translation adjustments net of tax impact of nil for the year ended December 31, 2020 (2019: nil and 2018: $(0.2) million)	16,596	570	(5,261)
Total comprehensive loss	**$ (108,428)**	**$ (123,631)**	**$ (88,565)**
Basic and diluted net loss per ordinary share	$ (2.81)	$ (3.11)	$ (2.34)
Weighted average shares used in computing basic and diluted net loss per ordinary share	44,466,365	39,999,450	35,639,745

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

uniQure N.V.

CONSOLIDATED STATEMENTS OF SHAREHOLDERS' EQUITY

	Ordinary shares		Additional paid-in capital	Accumulated other comprehensive (loss)/income	Accumulated deficit	Total shareholders' equity
	No. of shares	Amount	(in thousands, except share data)			
Balance at December 31, 2017	**31,339,040**	**$ 1,947**	**$ 566,530**	**$ (3,800)**	**$ (475,318)**	**$ 89,359**
Cumulative effect of retroactive implementation of ASC 606 Revenue recognition	—	—	—	1,802	23,116	24,918
Loss for the period	—	—	—	—	(83,304)	(83,304)
Other comprehensive loss	—	—	—	(5,261)	—	(5,261)
Follow-on public offering	5,175,000	309	138,052	—	—	138,361
Exercises of share options	425,074	19	4,741	—	—	4,760
Restricted and performance share units distributed during the period	409,948	24	(24)	—	—	—
Share-based compensation expense	—	—	10,708	—	—	10,708
Issuance of ordinary shares relating to employee stock purchase plan	2,591	—	65	—	—	65
Balance at December 31, 2018	**37,351,653**	**$ 2,299**	**$ 720,072**	**$ (7,259)**	**$ (535,506)**	**$ 179,606**
Loss for the period	—	—	—	—	(124,201)	(124,201)
Other comprehensive income	—	—	—	570	—	570
Follow-on public offering	5,625,000	311	242,363	—	—	242,674
Hercules warrants exercise	37,175	2	1,271	—	—	1,273
Exercise of share options	453,232	25	5,210	—	—	5,235
Restricted and performance share units distributed during the period	235,692	14	(14)	—	—	—
Share-based compensation expense	—	—	17,533	—	—	17,533
Issuance of ordinary shares relating to employee stock purchase plan	9,202	—	368	—	—	368
Balance at December 31, 2019	**43,711,954**	**$ 2,651**	**$ 986,803**	**$ (6,689)**	**$ (659,707)**	**$ 323,058**
Loss for the period	—	—	—	—	(125,024)	(125,024)
Other comprehensive income	—	—	—	16,596	—	16,596
Exercise of share options	498,678	29	7,169	—	—	7,198
Restricted and performance share units distributed during the period	560,986	31	(31)	—	—	—
Share-based compensation expense	—	—	21,831	—	—	21,831
Issuance of ordinary shares relating to employee stock purchase plan	6,181	—	246	—	—	246
Balance at December 31, 2020	**44,777,799**	**$ 2,711**	**$ 1,016,018**	**$ 9,907**	**$ (784,731)**	**$ 243,905**

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

uniQure N.V.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Cash flows from operating activities			
Net loss	$ (125,024)	$ (124,201)	$ (83,304)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation, amortization, and impairment losses	10,648	6,669	12,415
Share-based compensation expense	21,831	17,533	10,708
Change in fair value of derivative financial instruments and contingent consideration	(483)	2,530	(4,054)
Unrealized foreign exchange losses / (gains)	14,730	891	(5,502)
Deferred tax (income) / expense	(16,419)	-	231
Change in lease incentives	-	-	(330)
Change in deferred revenue	(33,642)	(4,999)	(8,462)
Changes in operating assets and liabilities:			
Accounts receivable and accrued income, prepaid expenses, and other current assets	(6,967)	(4,769)	1,578
Accounts payable	(2,701)	1,652	1,065
Accrued expenses, other liabilities, and operating leases	3,199	6,010	(382)
Net cash used in operating activities	(134,828)	(98,684)	(76,037)
Cash flows from investing activities			
Purchases of intangible assets	(2,213)	(996)	(1,861)
Purchases of property, plant, and equipment	(7,271)	(5,651)	(2,384)
Net cash used in investing activities	(9,484)	(6,647)	(4,245)
Cash flows from financing activities			
Proceeds from issuance of shares related to employee stock option and purchase plans	7,444	5,603	4,825
Proceeds from public offering of shares, net of issuance costs	-	242,718	138,361
Proceeds from loan increment	-	-	14,775
Proceeds from exercise of warrants	-	500	-
Net cash generated from financing activities	7,444	248,821	157,961
Currency effect on cash, cash equivalents and restricted cash	3,822	(106)	(2,187)
Net (decrease) / increase in cash, cash equivalents and restricted cash	(133,046)	143,384	75,491
Cash, cash equivalents and restricted cash at beginning of period	380,726	237,342	161,851
Cash, cash equivalents and restricted cash at the end of period	**$ 247,680**	**$ 380,726**	**$ 237,342**
Cash and cash equivalents	$ 244,932	$ 377,793	$ 234,898
Restricted cash related to leasehold and other deposits	2,748	2,933	2,444
Total cash, cash equivalents and restricted cash	**$ 247,680**	**$ 380,726**	**$ 237,342**
Supplemental cash flow disclosures:			
Cash paid for interest	$ (4,131)	$ (3,117)	$ (2,141)
Non-cash increase / (decrease) in accounts payables and accrued expenses and other current liabilities related to purchases of intangible assets and property, plant, and equipment	$ 630	$ 313	$ (48)

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

uniQure N.V.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. General business information

uniQure (the "Company") was incorporated on January 9, 2012 as a private company with limited liability (besloten vennootschap met beperkte aansprakelijkheid) under the laws of the Netherlands. The Company is a leader in the field of gene therapy and seeks to deliver to patients suffering from rare and other devastating diseases single treatments with potentially curative results. The Company's business was founded in 1998 and was initially operated through its predecessor company, Amsterdam Molecular Therapeutics Holding N.V ("AMT"). In 2012, AMT undertook a corporate reorganization, pursuant to which uniQure B.V. acquired the entire business and assets of AMT and completed a share-for-share exchange with the shareholders of AMT. Effective February 10, 2014, in connection with its initial public offering, the Company converted into a public company with limited liability (naamloze vennootschap) and changed its legal name from uniQure B.V. to uniQure N.V.

The Company is registered in the trade register of the Dutch Chamber of Commerce (Kamer van Koophandel) under number 54385229. The Company's headquarters are in Amsterdam, the Netherlands, and its registered office is located at Paasheuvelweg 25a, Amsterdam 1105 BP, the Netherlands and its telephone number is +31 20 240 6000. The Company's website address is www.uniqure.com.

The Company's ordinary shares are listed on the Nasdaq Global Select Market and trades under the symbol "QURE".

2. Summary of significant accounting policies

2.1 Basis of preparation

The Company prepared its consolidated financial statements in compliance with generally accepted accounting principles in the United States ("U.S. GAAP"). Any reference in these notes to applicable guidance is meant to refer to authoritative U.S. GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

The consolidated financial statements have been prepared under the historical cost convention, except for derivative financial instruments and contingent consideration, which are recorded at fair value through profit or loss.

The consolidated financial statements are presented in U.S. dollars, except where otherwise indicated. Transactions denominated in currencies other than U.S. dollars are presented in the transaction currency with the U.S. dollar amount included in parenthesis, converted at the foreign exchange rate as of the transaction date.

The consolidated financial statements presented have been prepared on a going concern basis based on the Company's cash and cash equivalents as of December 31, 2020 and the Company's budgeted cash flows for the twelve months following the issuance date.

2.2 Use of estimates

The preparation of consolidated financial statements, in conformity with U.S. GAAP and Securities and Exchange Commission ("SEC") rules and regulations, requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the consolidated financial statements and reported amounts of revenues and expenses during the reporting period. Estimates and assumptions are primarily made in relation to the treatment of the commercialization and license agreement entered into between the Company and CSL Behring LLC ("CSL Behring Agreement"), the December 1, 2020, amendment ("amended BMS CLA") of the 2015 collaboration and license agreement ("BMS CLA") between the Company and Bristol-Myers Squibb ("BMS"), share-based payments, valuation allowances for deferred tax assets, and accounting for operating leases under ASC 842. If actual results differ from the Company's estimates, or to the extent these estimates are adjusted in future periods, the Company's results of operations could either benefit from, or be adversely affected by, any such change in estimate.

2.3 Accounting policies

The principal accounting policies applied in the preparation of these consolidated financial statements are set out below. These policies have been consistently applied to all the years presented, unless otherwise stated.

2.3.1 Consolidation

The consolidated financial statements comprise the financial statements of the Company and its subsidiaries. Subsidiaries are all entities over which the Company has a controlling financial interest either through variable interest or through voting interest. Currently, the Company has no involvement with variable interest entities.

Inter-company transactions, balances, income, and expenses on transactions between uniQure entities are eliminated in consolidation. Profits and losses resulting from inter-company transactions that are recognized in assets are also eliminated. Accounting policies of subsidiaries have been changed where necessary to ensure consistency with the policies adopted by the Company.

2.3.2 Current versus non-current classification

The Company presents assets and liabilities in the consolidated balance sheets based on current and non-current classification.

The term current assets is used to designate cash and other assets, or resources commonly identified as those that are reasonably expected to be realized in cash or sold or consumed during the normal operating cycle of the business. The Company's normal operating cycle is twelve months. All other assets are classified as non-current.

The term current liabilities is used principally to designate obligations whose liquidation is reasonably expected to require the use of existing resources properly classifiable as current assets, or the creation of other current liabilities. Current liabilities are expected to be settled in the normal operating cycle. The Company classifies all other liabilities as non-current.

Deferred tax assets and liabilities are classified as non-current assets and liabilities, if any.

2.3.3 Foreign currency translation

The functional currency of the Company and each of its entities (except for uniQure Inc.) is the euro (€). This represents the currency of the primary economic environment in which the entities operate. The functional currency of uniQure Inc. is the U.S. dollar ($). The consolidated financial statements are presented in U.S. dollars.

Foreign currency transactions are measured and recorded in the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange gains and losses resulting from the settlement of such transactions and from the re-measurement of monetary assets and liabilities denominated in foreign currencies at exchange rates prevailing at balance sheet date are recognized in profit and loss.

Upon consolidation, the assets and liabilities of foreign operations are translated into the functional currency of the shareholding entity at the exchange rates prevailing at the balance sheet date; items of income and expense are translated at monthly average exchange rates. The consolidated assets and liabilities are translated from uniQure N.V.'s functional currency, euro, into the reporting currency U.S. dollar at the exchange rates prevailing at the balance sheet date; items of income and expense are translated at monthly average exchange rates. Issued capital and additional paid-in capital are translated at historical rates with differences to the balance sheet date rate recorded as translation adjustments in other comprehensive income / loss. The exchange differences arising on translation for consolidation are recognized in "accumulated other comprehensive income / loss". On disposal of a foreign operation, the component of other comprehensive income / loss relating to that foreign operation is recognized in profit or loss.

2.3.4 Fair value measurement

The Company measures certain assets and liabilities at fair value, either upon initial recognition or for subsequent accounting or reporting. *ASC 820, Fair Value Measurements and Disclosures* requires disclosure of methodologies used in determining the reported fair values and establishes a hierarchy of inputs used when available. The three levels of the fair value hierarchy are described below:

- Level 1 - Valuations based on unadjusted quoted prices in active markets for identical assets or liabilities that the Company can access at the measurement date.

- Level 2 - Valuations based on quoted prices for similar assets or liabilities in markets that are not active or models for which the inputs are observable, either directly or indirectly.

- Level 3 - Valuations that require inputs that reflect the Company's own assumptions that are both significant to the fair value measurement and are unobservable.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Items measured at fair value on a recurring basis include financial instruments and contingent consideration (Note 4, "Fair value measurement"). The carrying amount of cash and cash equivalents, accounts receivable from collaborators, prepaid expenses, other assets, accounts payable, accrued expenses and other current liabilities reflected in the consolidated balance sheets approximate their fair values due to their short-term maturities.

2.3.5 Notes to the consolidated statements of cash flows

The consolidated statements of cash flows have been prepared using the indirect method. The cash disclosed in the consolidated statements of cash flows is comprised of cash and cash equivalents. Cash and cash equivalents include bank balances, demand deposits and other short-term highly liquid investments (with maturities of less than three months at the time of purchase) that are readily convertible into a known amount of cash and are subject to an insignificant risk of fluctuation in value.

Cash flows denominated in foreign currencies have been translated at the average exchange rates. Exchange differences, if any, affecting cash and cash equivalents are shown separately in the consolidated statements of cash flows. Interest paid and received, and income taxes are included in net cash (used in) provided by operating activities.

2.3.6 Segment information

Operating segments are identified as a component of an enterprise for which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company views its operations and manages its business as one operating segment, which comprises the discovery, development, and commercialization of innovative gene therapies.

2.3.7 Net loss per share

The Company follows the provisions of *ASC 260, Earnings Per Share*. In accordance with these provisions, loss per share is calculated by dividing net loss by the weighted average number of ordinary shares outstanding during the period.

Diluted net loss per share reflects the dilution that would occur if share options or warrants to issue ordinary shares were exercised, or performance or restricted share units were distributed. However, potential ordinary shares are excluded if their effect is anti-dilutive. The Company currently has no dilutive securities due to the net loss position and as such, basic and diluted net loss per share are the same for the periods presented.

2.3.8 Impairment of long-lived assets

Long-lived assets, which include property, plant, and equipment and finite-lived intangible assets, are reviewed for impairment whenever events or changes in circumstances indicate that the carrying value of an asset or asset group may not be recoverable. Right-of-use assets are also reviewed for impairment in accordance with ASC 360. The recoverability of the carrying value of an asset or asset group depends on the successful execution of the Company's business initiatives and its ability to earn sufficient returns on approved products and product candidates. When such events or changes in circumstances occur, the Company assesses recoverability by determining whether the carrying value of such assets will be recovered through the undiscounted expected future cash flows. If the future undiscounted cash flows are less than the carrying amount of these assets, the Company recognizes an impairment loss based on the excess of the carrying value over the fair value of the assets. Fair value is determined through various valuation techniques, including discounted cash flow models, quoted market values, and third-party independent appraisals, as considered necessary.

Goodwill is not amortized but is evaluated for impairment within the Company's single reporting unit on an annual basis, during the fourth quarter, or more frequently if an event occurs or circumstances change that would more-likely-than-not reduce the fair value of the Company's reporting unit below its carrying amount. The Company performs the same quantitative analysis discussed above for long-lived assets and finite-lived intangible assets.

2.3.9 Property, plant, and equipment

Property, plant, and equipment is comprised mainly of laboratory equipment, leasehold improvements, construction-in-progress ("CIP") and office equipment. All property, plant and equipment is stated at cost less accumulated depreciation. CIP consists of capitalized expenses associated with construction of assets not yet placed into service. Depreciation commences on CIP once the asset is placed into service based on its useful life determined at that time.

Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed as incurred. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss on the transaction is recognized in the consolidated statements of operations and comprehensive loss.

Depreciation is calculated using the straight-line method over the estimated useful lives of the assets (or in the case of leasehold improvements a shorter lease term), which are as follows:

· Leasehold improvements	Between 10 – 15 years
· Laboratory equipment	5 years
· Office equipment	Between 3 – 5 years

2.3.10 Leases

The Company adopted ASC 842 using the modified retrospective approach with an effective date as of the beginning of the Company's fiscal year, January 1, 2019, to operating leases that existed on that date. Comparative financial information related to profit and loss and cash flows for the twelve-month period ended December 31, 2018, was not recast under the new standard, and continues to be presented under ASC 840.

The Company measured lease liabilities at the present value of the future lease payments as of January 1, 2019. The Company used an incremental borrowing rate to discount the lease payments. The Company derived the discount rate, adjusted for differences such as in the term and payment patterns, from the Company's loan from Hercules Technology Growth Capital, Inc ("Hercules Capital"), which was refinanced immediately prior to the January 1, 2019 adoption date in December 2018. The right-of-use asset is valued at the amount of the lease liability reduced by the remaining December 31, 2018 balance of lease incentives received. The lease liability is subsequently measured at the present value of the future lease payments as of the reporting date with a corresponding adjustment to the right-to-use asset. Absent a lease modification, the Company will continue to utilize the January 1, 2019, incremental borrowing rate.

The Company recognizes lease cost on a straight-line basis and presents these costs as operating expenses within the Consolidated statements of operations and comprehensive loss. The Company presents lease payments and landlord incentive payments within cash flows from operations within the Consolidated statements of cash flows.

The financial results for the years ended December 31, 2020 and 2019 are presented in accordance with ASC 842, while the financial results for the year ended December 31, 2018 are presented in accordance with the Company's historical accounting policy based on ASC 840.

2.3.11 Other (non) current assets

Deposits paid are either presented as other current assets or as other non-current assets based on duration of the underlying contractual arrangement. Deposits are classified as restricted cash and primarily relate to facility leases.

Contract assets are presented in other current assets or as other non-current assets based on the timing of the right to consideration.

2.3.12 Prepaid expenses

Prepaid expenses are amounts paid in the period, for which the benefit has not been realized, and include payments made for insurance and research and clinical contracts. The related expense will be recognized in the subsequent period as incurred.

2.3.13 Accounts receivable

Accounts receivables include amounts due from services provided to the Company's collaboration partner as well as unconditional rights to consideration from its collaboration partners.

2.3.14 Accounts payable and accrued expenses

Accounts payables are invoiced amounts related to obligations to pay for goods or services that have been acquired in the ordinary course of business from suppliers. Accounts payables are recognized at the amounts invoiced by suppliers.

Accrued expenses are recognized for goods or services that have been acquired in the ordinary course of business.

Contract liabilities are presented in accounts payable and accrued expenses.

2.3.15 Long-term debt

Long-term debt is initially recognized at cost and presented net of original issue discount or premium and debt issuance costs on the consolidated balance sheets. Amortization of debt discount and debt issuance costs is recognized as interest expense in profit and loss over the period of the debt, using the effective interest rate method.

2.3.16 Pensions and other post-retirement benefit plans

The Company has a defined contribution pension plan for all employees at its Amsterdam facility in the Netherlands, which is funded by the Company through payments to an insurance company, with individual accounts for each participants' assets. The Company has no legal or constructive obligation to pay further contributions if the plan does not hold sufficient assets to pay all employees the benefits relating to services rendered in the current and prior periods. The contributions are expensed as incurred. Prepaid contributions are recognized as an asset to the extent that a cash refund or a reduction in the future payments is available.

Starting in 2016, the Company adopted a qualified 401(k) Plan for all employees at its Lexington facility in the USA, which offers both a pre-tax and post-tax (Roth) component. Employees may contribute up to 50% of their pre-tax compensation, which is subject to IRS statutory limits for each calendar year. The Company matches $0.50 for every $1.00 contributed to the plan by participants up to 6% of base compensation. Employer contributions are recognized as they are contributed, as long as the employee is rendering services in that period. If employer contributions are made in periods after an individual retires or terminates, the estimated cost is accrued during the employee's service period.

2.3.17 Share-based compensation

The Company accounts for its share-based compensation awards in accordance with *ASC 718, Compensation-Stock Compensation.*

All the Company's share-based compensation plans for employees are equity-classified.

ASC 718 requires all share-based compensation to employees, including grants of employee options, restricted share units, performance share units and modifications to existing instruments, to be recognized in the consolidated statements of operations and comprehensive loss based on their grant-date fair values, net of an estimated forfeiture rate, over the requisite service period. Forfeitures of employee options are recognized as they occur. The requirements of ASC 718 are also applied to nonemployee share-based payment transactions except for specific guidance on certain inputs to an option-pricing model and the attribution of cost.

The Company uses a Hull & White option model to determine the fair value of option awards. The model captures early exercises by assuming that the likelihood of exercises will increase when the share-price reaches defined multiples of the strike price. This analysis is performed over the full contractual term.

2.3.18 Revenue recognition

The Company primarily generates revenue from its collaboration, research, and license agreements with its collaboration partner BMS for the development and commercialization of product candidates. The Company initially entered into these agreements in 2015 and amended them in 2020.

On January 1, 2018, the Company adopted new revenue recognition policies in accordance with ASC 606 using the modified retrospective approach. The Company evaluated the initial BMS CLA and determined that its performance obligations were as follows:

- Providing pre-clinical research activities ("Collaboration Revenue");
- Providing clinical and commercial manufacturing services for products ("Manufacturing Revenue"); and
- Providing access to its technology and know-how in the field of gene therapy as well as actively contributing to the target selection, the collaboration as a whole, the development during the target selection, the pre-clinical and the clinical phase through participating in joint steering committee and other governing bodies ("License Revenue").

As further discussed in Note 3, "Collaboration arrangements and concentration of credit risk", as a result of the December 2020 amended BMS CLA, the Company's performance obligation related to License Revenues was materially completed as of the date of the amendment effective date of December 1, 2020. The Company may still be required to provide pre-clinical research activities or clinical and commercial manufacturing services when BMS exercises its options for those services.

License Revenue

Until the December 2020 amendment of the BMS CLA the Company recognized License Revenue over the expected performance period based on its measure of progress towards the completion of certain activities related to its services. Following the December 2020 amendment of the BMS CLA the Company's performance was materially completed and it had satisfied its performance obligation (see Note 3, "Collaboration arrangements and concentration of credit risk", for a detailed discussion).

Collaboration and Manufacturing Revenue

The Company recognizes Collaboration Revenues associated to optional work orders it receives from BMS to provide analytical development and process development activities that are reimbursable by BMS in accordance with the BMS CLA as well as the amended BMS CLA.

BMS and the Company entered into a Master Clinical Supply Agreement in April 2017 for the Company to supply gene therapy products during the clinical phase as well as into a binding term sheet to supply gene therapy products during the commercial phase to BMS. In December 2020, BMS and the Company also entered into a Research Supply Agreement. Revenues from product sales will be recognized when earned. The Company will provide these services as it receives optional work orders from BMS in relation to such services.

2.3.19 Other income, other expense

The Company receives certain government and regional grants, which support its research efforts in defined projects, and include contributions towards the cost of research and development. These grants generally provide for reimbursement of approved costs incurred as defined in the respective grants and are deferred and recognized in the statements of operations and comprehensive loss over the period necessary to match them with the costs they are intended to compensate, when it is probable that the Company has complied with any conditions attached to the grant and will receive the reimbursement.

The Company's other income also consists of income from the subleasing of the Amsterdam facility while other expense consists of expenses incurred in relation to the subleasing income.

2.3.20 Research and development expenses

Research and development costs are expensed as incurred. Research and development expenses generally consist of laboratory research, clinical trials, statistical analysis, and report writing, regulatory compliance costs incurred with clinical research organizations and other third-party vendors (including post-approval commitments to conduct consistency and comparability studies). In addition, research and development expenses consist of start-up and validation costs related to the Company's Lexington facility and the development and improvement of the Company's manufacturing processes and methods. Furthermore, research and development costs include costs of materials and costs of intangible assets purchased from others for use in research and development activities. The costs of intangibles that are purchased from others for a particular research and development project and that have no alternative future uses (in other research and development projects or otherwise) are expensed as research and development costs at the time the costs are incurred or at the time when no alternative future use is identified.

2.3.21 Income taxes

Income taxes are recorded in accordance with *ASC 740, Income Taxes*, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the financial statement carrying amount and the tax bases of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more-likely-than-not that some or all the deferred tax assets will not be realized.

The benefits of tax positions are recognized only if those positions are more likely than not, based on the technical merits, to be sustained upon examination. Recognized tax positions are measured at the largest amount of tax benefit that is greater than 50 percent likely of being realized upon settlement. The determination as to whether the tax benefit will more-likely-than-not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2020, and 2019, the Company did not have any significant unrecognized tax benefits.

2.3.22 Recently Adopted Accounting Pronouncements

ASU 2018-13: Fair Value Measurement

In August 2018, the FASB issued ASU 2018-13, Fair Value Measurement (Topic 820) which modifies the disclosure requirements on fair value measurements. ASU 2018-13 is effective for fiscal years beginning after December 15, 2019, which for the Company was January 1, 2020. The new disclosure requirements for changes in unrealized gains and losses in other comprehensive income for recurring Level 3 measurements, the range and weighted average of significant unobservable inputs and the amended requirements for the narrative description of measurement uncertainty should be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments should be applied retrospectively. ASU 2018-13 did not have a material impact on the Company's consolidated financial statements.

Recent Accounting Pronouncements Not Yet Effective

None.

3. Collaboration arrangements and concentration of credit risk

CSL Behring collaboration

On June 24, 2020, uniQure biopharma B.V., a wholly-owned subsidiary of uniQure N.V., entered into the CSL Behring Agreement with CSL Behring LLC, ("CSL Behring"), pursuant to which CSL Behring will receive exclusive global rights to etranacogene dezaparvovec, the Company's investigational gene therapy for patients with hemophilia B, (the "Product").

Under the terms of the CSL Behring Agreement, the Company will receive a $450.0 million upfront cash payment upon the closing of the CSL Behring Agreement and be eligible to receive up to $1.6 billion in additional payments based on regulatory and commercial milestones. The CSL Behring Agreement also provides that the Company will be eligible to receive tiered double-digit royalties in a range of up to a low-twenties percent of net sales of the Product based on sales thresholds.

Pursuant to the CSL Behring Agreement, the Company will be responsible for the completion of the HOPE-B clinical trial, manufacturing process validation, and the manufacturing supply of the Product until such time that these capabilities may be transferred to CSL Behring or its designated contract manufacturing organization. Concurrently with the execution of the CSL Behring Agreement, the Company and CSL Behring entered into a development and commercial supply agreement, pursuant to which, among other things, the Company will supply the Product to CSL Behring at an agreed-upon price. Clinical development and regulatory activities performed by the Company pursuant to the CSL Behring Agreement will be reimbursed by CSL Behring. CSL Behring will be responsible for global regulatory submissions and commercialization requirements for the Product.

The effectiveness of the transactions contemplated by the CSL Behring Agreement is contingent on completion of review under antitrust laws in the United States, Australia, and the United Kingdom, and certain provisions of the CSL Behring Agreement will not become effective until after we receive all such regulatory approvals. As of December 31, 2020, such regulatory approvals had not been received in all jurisdictions.

As of December 31, 2020, the Company concluded it has no enforceable right to the upfront payment, the regulatory and sale milestone payments, or the royalties (together "CSL Behring License Revenue") that the Company may receive in accordance with the CSL Behring Agreement, as all payments are contingent upon the successful completion of reviews under the Hart-Scott-Rodino Antitrust Improvements Act of 1976. Therefore, the Company determined it will not recognize any revenue in relation to the CSL Behring License Revenue, in accordance with ASC 606 during the year ended December 31, 2020. In accordance with its existing license and other agreements, the Company is contractually required to pay in total a low to high single digit percentage of any upfront payment to its licensors and financial advisor ("License Fees"). The Company did not record any License Fees in the year ended December 31, 2020, as the Company had not recognized the upfront payment as this date.

The Company incurred $2.1 million of expenses related to the obligations related to the CSL Behring Agreement that had not been satisfied as of December 31, 2020. The Company capitalized these expenses as contract fulfillment costs (presented within Other current assets). As of December 31, 2020, the Company also recognized a $2.1 million receivable (presented within Accounts receivable) from CSL Behring for expenses for which it has a right of reimbursement as well as a contract liability (presented within Accrued expenses and other current liabilities) for the same amount. In accordance with ASC 606 it cannot recognize any CSL Behring License Revenue as of this date.

Bristol-Myers Squibb collaboration

2015 Agreement

In May 2015, the Company entered into the BMS CLA and various related agreements with BMS, which the Company collectively refers to as the BMS CLA, which provided BMS with exclusive access to the Company's gene therapy technology platform for the research, development and commercialization of therapeutics aimed at multiple Collaboration Targets. The initial four-year research term under the collaboration terminated on May 21, 2019. During the initial research term of the BMS CLA, the Company supported BMS in discovery, non-clinical, analytical and process development efforts in respect of the Collaboration Targets. For any Collaboration Targets that may be advanced, the Company will be responsible for manufacturing of clinical and commercial supplies. BMS reimbursed the Company for all its research and development costs in support of the collaboration, and will lead development, regulatory and commercial activities for any Collaboration Targets that may be advanced. The BMS CLA initially provided that the Company and BMS could potentially have collaborated on up to ten Collaboration Targets in total.

BMS initially designated four Collaboration Targets, including S100A1 for congestive heart failure ("AMT-126"). In October 2018, the Company and BMS completed a heart function proof-of-concept study of AMT-126 in a pre-clinical, diseased animal model. The data did not show a benefit on heart function at six months and, consequently, work on S100A1 was discontinued. The Company impaired a $5.4 million acquired research and development asset associated with the program and released a contingent liability of $3.8 million related to the acquisition of the asset to income in the year ended December 31, 2018. In April 2019, BMS designated a new cardiovascular Collaboration Target to replace S100A1. As a result, BMS had designated a total of four Collaboration Targets as of December 31, 2019.

2020 Amendment

In February 2019, BMS requested a one-year extension of the initial research term. In April 2019, following an assessment of the progress of the collaboration and the Company's expanding proprietary programs, the Company notified BMS that the Company did not intend to agree to an extension of the initial research term but rather preferred to restructure or amend the collaboration to reduce or eliminate certain of the Company's obligations under it.

On December 1, 2020, the Company and BMS entered into the amended BMS CLA. Under the amended BMS CLA, BMS is limited to four Collaboration Targets. For a period of one-year from the effective date of the amended BMS CLA, BMS may replace up to two of these four Collaboration Targets with up to two new targets in the field of cardiovascular disease. The Company continues to be eligible to receive research, development, and regulatory milestone payments of up to $217.0 million for each Collaboration Target, if defined milestones are achieved.

BMS is no longer entitled to designate the fifth to tenth Collaboration Targets and as such the Company's remaining obligations under the amended BMS CLA are substantially reduced. The Company is no longer entitled to receive up to an aggregate $16.5 million in target designation payments for the research, development and regulatory milestone payments associated with the fifth to tenth Collaboration Targets.

For as long as any of the four Collaboration Targets are being advanced, BMS may place a purchase order to be supplied with research, clinical and commercial supplies. Subject to the terms of the amended BMS CLA, BMS has the right to terminate the research, clinical and commercial supply relationships, and has certain remedies for failures of supply, up to and including technology transfer for any such failure that otherwise cannot be reasonably resolved. Both BMS and the Company may agree to a technology transfer of manufacturing capabilities pursuant to the terms of the amended BMS CLA.

The amended BMS CLA does not extend the initial research term. BMS may place purchase orders to provide limited services primarily related to analytical and development efforts in respect of the four Collaboration Targets. BMS may request such services for a period not to exceed the earlier of (i) the completion of all activities under a Research Plan and (ii) either (A) three years after the last replacement target has been designated by BMS during the one year replacement period following the amended BMS CLA effective date or (B) three years if no replacement targets are designated during this one year period and BMS continues to reimburse the Company for these services.

The Company evaluated the impact of the amendment of the BMS CLA in relation to its performance obligation related to:

- Providing access to its technology and know-how in the field of gene therapy and participating in joint steering committee and other governing bodies (materially satisfied as of December 1, 2020) ("License Revenue").

The Company did not identify any new distinct performance obligations and determined the amended BMS CLA did not represent a separate contract in accordance with ASC 606. The Company evaluated the effect the modification has on its measure of progress towards the completion of its performance obligation related to License Revenue and recorded an adjustment to License Revenue as of December 1, 2020.

Services to BMS are rendered by the Dutch operating entity. Total collaboration and license revenue generated with BMS are as follows (presented as revenue from a related party until November 30, 2020, and as revenue from December 1, 2020 onwards):

	Years ended December 31,		
	2020	2019	2018
	(in thousands)		
Bristol Myers Squibb	$ 37,514	$ 7,281	$ 11,284
Total	**$ 37,514**	**$ 7,281**	$ **11,284**

Amounts owed by BMS in relation to the Collaboration and License Revenue are as follows (presented as "Accounts receivables" as of December 31, 2020 and as "Accounts receivable from related party" as of December 31, 2019):

	December 31, 2020	December 31, 2019
	(in thousands)	
Bristol Myers Squibb	$ 4,536	$ 947
Total	**$ 4,536**	**$ 947**

Collaboration Revenue

The Company recognizes collaboration revenues associated with Collaboration Target-specific pre-clinical analytical development and process development activities that are reimbursable by BMS under the BMS CLA and the amended BMS CLA as well as other related agreements. Collaboration Revenue related to these contracted services is recognized when performance obligations are satisfied.

The Company generated $0.2 million collaboration revenue for the year ended December 31, 2020 (December 31, 2019: $2.3 million; December 31, 2018: $3.8 million).

License Revenue

The Company recognized $33.0 million of License Revenue for the year ended December 31, 2020 (December 31, 2019: $5.0 million, December 31, 2018: $7.5 million).

On May 21, 2015, the Company recorded a $60.1 million upfront payment and in August 2015 it recorded a $15.0 million payment it received from BMS in relation to the designation of the second, third and fourth Collaboration Targets. The Company recognizes License Revenue over the expected performance period based on its measure of progress towards the completion of certain activities related to its services. The Company determines such progress by comparing activities performed at the end of each reporting period with total activities expected to be performed. The Company estimates total expected activities using several unobservable inputs, such as the probability of BMS designating additional targets, the probability of successfully completing each phase and estimated time required to provide services during the various development stages. The estimation of total services at the end of each reporting period involves considerable judgement.

The amount of services the Company expects to provide is significantly impacted by the number of Collaboration Targets that it estimates BMS would pursue. As a result of the December 1, 2020 amendment of the BMS CLA the Company no longer is required to potentially provide any services in relation to six additional targets that BMS might have designated. The Company determined its remaining performance obligation is immaterial. The Company adjusted its measure of progress towards the completion of its activities related to its services as of the December 1, 2020 modification date accordingly. The Company recognized the remaining balance of unrecognized License Revenue as of November 30, 2020 of $27.8 million in profit and loss during the year ended December 31, 2020 as License Revenue from a related party.

The Company includes variable consideration related to any research, development, and regulatory milestone payments, in the transaction price once it is considered probable that including these payments in the transaction price would not result in the reversal of cumulative revenue recognized. Due to the significant uncertainty surrounding the development of gene-therapy product candidates and the dependence on BMS's performance and decisions, the Company does not currently (with below exception) consider this probable.

On December 17, 2020 BMS designated one of the four Collaboration Targets as a candidate to advance into IND-enabling studies entitling the Company to receive a $4.4 million research milestone payment. The Company recorded the $4.4 million as License Revenue in the twelve-month period ended December 31, 2020.

The Company recognizes License Revenue related to product sales by BMS from any of the Collaboration Targets when the sales occur. The Company is eligible to receive net sales-based milestone payments and tiered mid-single to low double-digit royalties on product sales. The royalty term is determined on a licensed-product-by-licensed-product and country-by-country basis and begins on the first commercial sale of a licensed product in a country and ends on the expiration of the last to expire of specified patents or regulatory exclusivity covering such licensed product in such country or, with a customary royalty reduction, ten years after the first commercial sale if there is no such exclusivity.

4. Fair value measurement

The Company measures certain financial assets and liabilities at fair value, either upon initial recognition or for subsequent accounting or reporting.

The carrying amount of cash and cash equivalents, accounts receivable from collaborators, prepaid expenses, other assets, accounts payable, accrued expenses and other current liabilities reflected in the consolidated balance sheets approximate their fair values due to their short-term maturities.

The Company's only material financial assets measured at fair value using Level 1 inputs is cash and cash equivalents.

The liability measured at fair value using Level 3 inputs as of December 31, 2020 was the derivative financial instrument. The Company had recorded derivative financial instruments as of December 31, 2019, that were measured at fair value using Level 3 inputs. Changes in Level 3 items during the years ended December 31, 2020, 2019 and 2018 are as follows:

	Contingent consideration	Derivative financial instruments	Total
		(in thousands)	
Balance at December 31, 2017	**$ 3,964**	**$ 1,635**	**$ 5,599**
Net gains recognized in profit or loss	(3,846)	(208)	(4,054)
Currency translation effects	(118)	(52)	(170)
Balance at December 31, 2018	**$ —**	**$ 1,375**	**$ 1,375**
Net losses recognized in profit or loss	—	2,530	2,530
Exercise of Hercules warrants	—	(770)	(770)
Currency translation effects	—	(60)	(60)
Balance at December 31, 2019	**$ —**	**$ 3,075**	**$ 3,075**
Net gains recognized in profit or loss	—	(2,300)	(2,300)
Derecognition of warrants	—	(796)	(796)
Recognition of derivative financial liability of CoC-payment	—	2,613	2,613
Currency translation effects	—	53	53
Balance at December 31, 2020	**$ —**	**$ 2,645**	**$ 2,645**

Derivative financial instruments

The Company issued derivative financial instruments related to its collaboration with BMS and in relation to the issuance of the Hercules loan facility.

Derivative financial instruments BMS

Pursuant to the BMS CLA, the Company in 2015 granted BMS two warrants that were subsequently terminated in connection with the amendment to the BMS CLA on December 1, 2020. The Company granted to BMS:

- A warrant that allowed BMS to purchase a specific number of the Company's ordinary shares such that its ownership would have equaled 14.9% immediately after such purchase ("1st warrant"). The 1st warrant could have been exercised on the later of (i) the date on which the Company received from BMS the Target Designation Fees (as defined in the BMS CLA) associated with the first six new targets (a total of seven Collaboration Targets); and (ii) the date on which BMS designated the sixth new target (the seventh Collaboration Target); and
- A warrant that allowed BMS to purchase a specific number of the Company's ordinary shares such that its ownership would have equaled 19.9% immediately after such purchase ("2nd warrant" and together with 1st warrant, the "warrants"). The warrant could have been exercised on the later of (i) the date on which the Company received from BMS the Target Designation Fees associated with the first nine new targets (a total of ten Collaboration Targets); and (ii) the date on which BMS designated the ninth new target (the tenth Collaboration Target).

On December 1, 2020, the Company derecognized the warrants when these were terminated in accordance with the amended BMS CLA.

Pursuant to the terms of the BMS CLA the exercise price in respect of each warrant was equal to the greater of (i) the product of (A) $33.84, multiplied by (B) a compounded annual growth rate of 10% (or approximately $57.32 as of November 30, 2020) and (ii) the product of (A) 1.10 multiplied by (B) the weighted average volume price ("VWAP") for the 20 trading days ending on the date that is five trading days prior to the date of a notice of exercise delivered by BMS.

The fair value of the warrants as of December 31, 2019 was $3.1 million. During the year ended December 31, 2020, the Company recognized a $3.1 million gain in non-operating income / expense (December 31, 2019: $2.3 million loss; December 31, 2018: $0.5 million gain) related to fair value changes of the BMS warrants. The gain recognized in the year ended December 31, 2020 includes $0.8 million from the derecognition of the BMS warrants on December 1, 2020.

The Company used Monte-Carlo simulations to determine the fair market value of the BMS warrants. The valuation model incorporated several inputs, the risk-free rate adjusted for the period affected, an expected volatility based on historical Company volatility, the expected yield on any dividends and management's expectations on the timelines of reaching certain defined trigger events for the exercising of the warrants, as well as management's expectations regarding the number of ordinary shares that would be issued upon exercise of the warrants. All of these represent Level 3 inputs. Additionally, the model assumed BMS would exercise the warrants only if it was financially rational to do so.

The warrants could only have been exercised following the occurrence of events contractually defined in the warrant agreements. The probability of the occurrence of these events represented another significant unobservable input used in the calculation of the fair value of the warrants.

On December 1, 2020, the Company and BMS terminated the BMS warrants and agreed that upon the consummation of a change of control transaction of uniQure that occurs prior to December 1, 2026 or BMS' delivery of a target cessation notice for all four Collaboration Targets, uniQure (or its third party acquirer) shall pay to BMS a one-time, non-refundable, non-creditable cash payment of $70.0 million, provided that (x) if $70.0 million is greater than five percent (5.0%) of the net proceeds (as contractually defined) from such change of control transaction, the payment shall be an amount equal to five percent of such net proceeds, and (y) if $70.0 million is less than one percent of such net proceeds, the change of control payment shall be an amount equal to one percent of such net proceeds ("CoC-payment"). The Company has not consummated any change of control transaction as of December 31, 2020 that would obligate it to make a CoC-payment. The Company determined that the CoC-payment should be recorded as a derivative financial liability as of December 1, 2020 and that subsequent changes in the fair market value of this derivative financial liability should be recorded in profit and loss. The fair market value of the derivative financial liability is materially impacted by probability that market participants assign to the likelihood of the occurrence of a change of control transaction that would give rise to a CoC-payment. This probability represents an unobservable input. The Company determined the fair market value of the derivative financial liability by using a present value model based on expected cash flow. The expected cash flows are materially impacted by the probability that market participants assign to the likelihood of the occurrence of a change of control event within the biotechnology industry. The Company estimated this unobservable input using the best information available as of December 1, 2020 and December 31, 2020. The Company obtained reasonably available market information that it believed market participants would use in determining the likelihood of the occurrence of a change-of control transaction within the biotechnology industry. Selecting and evaluating market information involves considerable judgement and uncertainty. Based on all such information and its judgment the Company estimated that the fair market value of the derivative financial liability (presented within "Other non-current liabilities") as of December 1, 2020 and December 31, 2020 was $2.6 million. The Company recorded a $2.6 million loss within "Other non-operating expenses" in the twelve-month period ended December 31, 2020 related to the initial recognition of this derivative financial liability.

Hercules loan facility

On June 14, 2013, the Company entered into a venture debt loan facility (the "Original Facility") with Hercules (see Note 8, "Long-term debt") pursuant to a Loan and Security Agreement (the "Loan Agreement"), which included a warrant maturing on February 5, 2019. The warrant was not closely related to the host contract and was accounted for separately as a derivative financial liability measured at fair value though profit or loss. The warrant included in the Original Facility remained in place following the 2014, 2016 and 2018 amendments of the loan. The Hercules warrants were exercised as of February 1, 2019. The Company issued 37,175 ordinary shares at $34.25 following the exercise of all Hercules warrants and receipt of $0.5 million from Hercules. During the year ended December 31, 2020, the Company recognized no more gains or losses in other non-operating income / (expense) (December 31, 2019: $0.2 million loss; December 31, 2018: $0.3 million loss) related to fair value changes of the Hercules warrants.

Contingent consideration

In connection with the Company's acquisition of the InoCard business ("InoCard") in 2014, the Company recorded contingent consideration related to amounts potentially payable to InoCard's former shareholders. The amounts payable in accordance with the sale and purchase agreement (as amended in August 2017) were contingent upon realization of milestones associated with its S100A1 protein research program. Following the discontinuation of the research program the Company since 2018 no longer expects to realize those milestones and recorded a $3.8 million gain within research and development expenses for the year ended December 31, 2018, to release the liability to profit and loss.

5. Property, plant, and equipment, net

The following table presents the Company's property, plant, and equipment as of December 31:

	December 31, 2020	December 31, 2019
	(in thousands)	
Leasehold improvements	$ 37,849	$ 34,611
Laboratory equipment	22,106	18,232
Office equipment	5,025	4,212
Construction-in-progress	2,574	341
Total property, plant, and equipment	67,554	57,396
Less accumulated depreciation	(35,226)	(28,625)
Property, plant and equipment, net	**$ 32,328**	**$ 28,771**

Total depreciation expense was $5.7 million for the year ended December 31, 2020 (December 31, 2019: $6.0 million, December 31, 2018: $6.5 million). Depreciation expense is allocated to research and development expenses to the extent it relates to the Company's manufacturing facility and equipment and laboratory equipment. All other depreciation expenses are allocated to selling, general and administrative expense.

The following table summarizes property, plant, and equipment by geographic region.

	December 31, 2020	December 31, 2019
	(in thousands)	
Lexington, Massachusetts (United States of America)	$ 15,949	$ 15,490
Amsterdam (the Netherlands)	16,379	13,281
Total	**$ 32,328**	**$ 28,771**

6. Right-of-use asset and lease liabilities

The Company adopted ASU 2016-02 "Leases (Topic 842)" as well as ASU 2018-10 and ASU 2018-11, which both relate to improvements to ASC 842. The Company adopted the standard using the modified retrospective approach with an effective date as of the beginning of the Company's fiscal year, January 1, 2019 ("new lease accounting standard"). The standard requires the balance sheet recognition for leases. Prior years were not recast under the new standard and therefore, those amounts are presented in accordance with the requirements of the previously effective lease standard ASC 840 ("historic lease accounting standard"). The Company elected to utilize practical expedients available for expired or existing contracts which allowed the Company to carryforward historical assessments of (1) whether contracts are or contain leases, (2) lease classification, and (3) initial direct costs.

The Company's most significant leases relate to office and laboratory space under the following operating lease agreements:

Lexington, Massachusetts / United States

In July 2013, the Company entered into a lease for a facility in Lexington, Massachusetts, United States. The term of the lease commenced in November 2013, was set for 10 years starting from the 2014 rent commencement date and is non-cancellable. Originally, the lease for this facility had a termination date of 2024. In November 2018, the term was expanded by five years to June 2029. The lease continues to be renewable for two subsequent five-year terms. Additionally, the lease was expanded to include an additional 30,655 square feet within the same facility and for the same term. The lease of the expansion space commenced on June 1, 2019.

The contractually fixed annual increase of lease payments through 2029 for both the extension and expansion lease have been included in the lease payments.

Amsterdam / The Netherlands

In March 2016, the Company entered into a 16-year lease for a facility in Amsterdam, the Netherlands and amended this agreement in June 2016. The Company consolidated its three Amsterdam sites into the new site at the end of May 2017. The lease for the new facility terminates in 2032, with an option to extend in increments of five-year periods. The lease contract includes variable lease payments related to annual increases in payments based on a consumer price index.

On December 1, 2017, the Company entered into an agreement to sub-lease three of the seven floors of its Amsterdam facility for a ten-year term ending on December 31, 2027, with an option for the sub-lessee to extend until December 31, 2031. In February 2020, the Company amended the agreement to sub-lease to take back one of the three floors effective March 1, 2020. The fixed lease payments to be received during the remaining term under the agreement to sub-lease amount to $6.6 million (EUR 5.4 million) as of December 31, 2020.

Operating lease liabilities

The components of lease cost in accordance with the new lease accounting standard were as follows:

	Year ended December 31,	
	2020	2019
	(in thousands)	
Operating lease cost	$ 5,052	$ 4,474
Variable lease cost	607	507
Sublease income	(904)	(1,053)
Total lease cost	**$ 4,755**	**$ 3,928**

The rent expense in accordance with the historical lease accounting standard for the year ended December 31, 2018, was calculated on a straight-line basis over the term of the lease and considered $12.2 million of lease incentives received. Aggregate rent expense was as follows:

	Year ended December 31, 2018
	(in thousands)
Rent expense - Lexington	$ 1,583
Rent expense - Amsterdam	1,667
Total lease cost	**$ 3,250**

The table below presents the lease-related assets and liabilities recorded on the Consolidate balance sheets in accordance with the new lease accounting standard.

	December 31, 2020	December 31, 2019
	(in thousands)	
Assets		
Operating lease right-of-use assets	**$ 26,086**	**26,797**
Liabilities		
Current		
Current operating lease liabilities	5,524	5,865
Non-current		
Non-current operating lease liabilities	30,403	31,133
Total lease liabilities	**$ 35,927**	**36,998**

Other information

The weighted-average remaining lease term as of December 31, 2020, is 9.4 years, compared to 10.3 years as of December 31, 2019, and the weighted-average discount rate as of December 31, 2020, is 11.37%, compared to 11.33% as of December 31, 2019. The Company derived the weighted-average discount rate, adjusted for differences such as in the term and payment patterns, from the Company's loan from Hercules capital which was refinanced immediately prior to the January 1, 2019, adoption date in December 2018.

The table below presents supplemental cash flow and non-cash information related to leases required in accordance with the new lease accounting standard.

	Year ended December 31,	
	2020	2019
	(in thousands)	
Operating cash flows for operating leases [1]	$ 5,769	$ 4,717

(1) The Company has received $1.5 million of landlord incentive payments for the year ended December 31, 2019, which are not included in the cash paid amounts.)

The Company did not obtain any right-of-use assets in exchange for the lease obligations during the year ended December 31, 2020. Besides the initial recognition of operating right-of-use assets of $19.0 million upon adoption of the new lease standards on January 1, 2019, the Company obtained $9.0 million of additional right-of-use assets in exchange for lease obligations during the year ended December 31, 2019.

Undiscounted cash flows

The table below reconciles the undiscounted cash flows as of December 31, 2020, for each of the first five years and the total of the remaining years to the operating lease liabilities recorded on the Consolidated balance sheet as of December 31, 2020 in accordance with the new lease accounting standard.

	Lexington	Amsterdam[1]	Total
		(in thousands)	
2021	$ 3,455	$ 2,069	$ 5,524
2022	3,552	2,069	5,621
2023	3,650	2,069	5,719
2024	4,146	2,069	6,215
2025	4,465	2,069	6,534
Thereafter	16,279	12,239	28,518
Total lease payments	$ 35,547	$ 22,584	$ 58,131
Less: amount of lease payments representing interest payments	(12,576)	(9,628)	(22,204)
Present value of lease payments	22,971	12,956	35,927
Less: current operating lease liabilities	(3,455)	(2,069)	(5,524)
Non-current operating lease liabilities	**$ 19,516**	**$ 10,887**	**$ 30,403**

(1) Payments are due in EUR and have been translated at the foreign exchange rate as of December 31, 2020, of $1.23 / €1.00)

7. Intangible assets

a. Acquired licenses

The following table presents the Company's acquired licenses as of December 31:

	December 31, 2020	December 31, 2019
	(in thousands)	
Licenses	$ 5,660	$ 8,317
Less accumulated amortization and impairment	(2,299)	(2,890)
Licenses, net	**$ 3,361**	**$ 5,427**

All intangible assets are owned by uniQure biopharma B.V, a subsidiary of the Company. The acquired licenses have a weighted average remaining life of 8.5 years as of December 31, 2020.

During the year ended December 31, 2020, the Company capitalized $2.2 million of expenditures related to costs incurred in relation to rights to exclusively evaluate certain technologies during a two-year period that commenced on February 1, 2020. During the same period, the Company disposed of a number of licenses determined to have no alternative future use. During the year ended December 31, 2019, the Company capitalized $1.0 million of expenditures related to contractual milestone payments under existing license agreements.

As of December 31, 2020, the estimated future amortization expense for each of the five succeeding years and the period thereafter is as follows:

Years	Amount
	(in thousands)
2021	$ 1,277
2022	427
2023	144
2024	144
2025	144
Thereafter	1,225
Total	**$ 3,361**

The amortization expense related to licenses for the year ended December 31, 2020 was $4.6 million (December 31, 2019: $0.6 million; December 31, 2018: $0.4 million). The impairment expense related to licenses for the year ended December 31, 2020 was $0.3 million (December 31, 2019: $0.0 million; December 31, 2018 $0.1 million).

b. Acquired research and development

The Company acquired research and development assets as part of its acquisition of InoCard in July 2014. Based on the review of pre-clinical data associated with those assets, the Company does not expect that it will pursue further research related to those assets. Accordingly, the Company recorded a $5.4 million impairment loss within research and development expenses in the year ended December 31, 2018, to reduce the asset's carrying amount to its fair value of nil.

8. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities include the following items:

	December 31, 2020	December 31, 2019
	(in thousands)	
Accruals for services provided by vendors-not yet billed	$ 8,269	$ 5,425
Personnel related accruals and liabilities	7,687	7,032
Contract liability (see Note 3. Collaboration arrangements)	2,082	—
Total	**$ 18,038**	**$ 12,457**

9. Long-term debt

On June 14, 2013, the Company entered into a venture debt loan facility with Hercules, which was amended and restated on June 26, 2014, and again on May 6, 2016 ("2016 Amended Facility"). On December 6, 2018, the Company signed an amendment to the Second Amended and Restated Loan and Security Agreement that both refinanced the then-existing $20.0 million 2016 Amended Facility and provided an additional unconditional commitment of $15.0 million as well as a conditional commitment of $15.0 million that expired on June 30, 2020 (the "2018 Amended Facility"). At signing of the 2018 Amended Facility, the Company drew down an additional $15.0 million for a total of $35.0 million outstanding. The 2018 Amended Facility extended the loan's maturity date from May 1, 2020 until June 1, 2023. The interest-only period was initially extended from November 2018 to January 1, 2021, and was further extended to January 1, 2022, as a result of meeting the provision in the 2018 Amended Facility of raising more than $90.0 million in equity financing in September 2019. The Company is required to repay the facility in equal monthly installments of principal and interest between the end of the interest-only period and the maturity date. The interest rate continues to be adjustable and is the greater of (i) 8.85% or (ii) 8.85% plus the prime rate less 5.50% per annum.

Under the 2018 Amended Facility, the Company paid a facility fee of 0.50% of the $35.0 million outstanding as of signing and owes a back-end fee of 4.95% of the outstanding debt. In addition, in May 2020 the Company paid a back-end fee of $1.0 million in relation to the 2016 Amended Facility.

The amortized cost (including interest due presented as part of accrued expenses and other current liabilities) of the 2018 Amended Facility was $35.9 million as of December 31, 2020, compared to $36.3 million as of December 31, 2019, and is recorded net of discount and debt issuance costs. The foreign currency gain on the loan was $3.1 million in 2020 (2019: loss of $0.7 million; 2018: loss of $0.9 million). The fair value of the loan approximates its carrying amount. Inputs to the fair value of the loan are considered Level 3 inputs.

Interest expense recorded during the years ended December 31 was as follows:

Years	Amount (in millions)
2020	$ 3.7
2019	3.7
2018	2.0

As a covenant in the 2018 Amended Facility, the Company has periodic reporting requirements and is required to keep a minimum cash balance deposited in bank accounts in the United States, equivalent to the lesser of (i) 65% of the outstanding balance of principal due or (ii) 100% of worldwide cash and cash equivalents. This restriction on cash and cash equivalents only relates to the location of the cash and cash equivalents, and such cash and cash equivalents can be used at the discretion of the Company. In combination with other covenants, the 2018 Amended Facility restricts the Company's ability to, among other things, incur future indebtedness and obtain additional debt financing, to make investments in securities or in other companies, to transfer assets, to perform certain corporate changes, to make loans to employees, officers, and directors, and to make dividend payments and other distributions. The Company secured the facilities by directly or indirectly pledging its total assets of $340.4 million with the exception of $115.2 million of cash and cash equivalents and other current assets held by uniQure N.V.

The 2018 Amended Facility contains provisions that include the occurrence of a material adverse effect, as defined therein, which would entitle Hercules to declare all principal, interest and other amounts owed by the Company immediately due and payable. As of December 31, 2020, the Company was in compliance with all covenants and provisions.

The aggregate maturities of the loan, including $7.4 million of coupon interest payments and financing fees, for each of the 29 months after December 31, 2020, are as follows (prior to the January 2021 loan amendment – see Note 18, "Subsequent events"):

Years	Amount (in thousands)
2021	$ 3,141
2022	25,002
2023	14,269
Total	**$ 42,412**

10. Shareholders' equity

As of December 31, 2020, the Company's authorized share capital is €3.0 million (or $3.7 million when translated at an exchange rate as of December 31, 2020, of $1.23 / €1.00), divided into 60,000,000 ordinary shares, each with a nominal value of €0.05. Under Dutch law, the authorized share capital is the maximum capital that the Company may issue without amending its articles of association.

All ordinary shares issued by the Company were fully paid. Besides the minimum amount of share capital to be held under Dutch law, there are no distribution restrictions applicable to the equity of the Company.

As of December 31, 2020, and 2019 and 2018 the Company's reserves were restricted for payment of dividends for an accumulated foreign currency translation gain of $9.9 million in 2020 and accumulated foreign currency translation losses of $6.7 million and $7.3 million in 2019 and 2018, respectively.

On September 10, 2019, the Company completed a follow-on public offering of 4,891,305 ordinary shares at a public offering price of $46.00 per ordinary share, and on September 13, 2019, the Company completed the sale of an additional 733,695 ordinary shares at a public offering price of $46.00 per ordinary share pursuant to the exercise by the underwriters of the option to purchase additional ordinary shares, resulting in total gross proceeds to the Company of $258.8 million. The net proceeds to the Company from this offering were $242.7 million, after deducting underwriting discounts and commissions and other offering expenses payable by the Company. The Company deducted $0.6 million of expenses incurred related to this offering from additional paid-in capital in the accompanying consolidated balance sheets and reflected this within the proceeds from public offering of shares, net of issuance costs within the cash flows from financing activities.

On May 7, 2018, the Company completed a follow-on public offering of 5,175,000 ordinary shares at a public offering price of $28.50 per ordinary share, resulting in gross proceeds to the Company of $147.5 million. The net proceeds to the Company from this offering were $138.4 million, after deducting underwriting discounts and commissions and other offering expenses payable by the Company. The Company deducted $0.2 million of expenses incurred related to this offering from additional paid-in capital in the accompanying consolidated balance sheet and reflected this within the proceeds from public offering of shares, net of issuance costs within the cash flows from financing activities.

In February 2019, the Company issued 37,175 ordinary shares to Hercules pursuant to exercised warrants for $0.5 million in aggregate cash consideration. The Company deemed the sale and issuance of these shares to be exempt from registration under the Securities Act in reliance on Regulation S of the Securities Act, as an offshore offering of securities and such shares were issued as restricted shares. Hercules represented to us that they were in compliance with the requirements of Regulation S.

11. Share-based compensation

Share-based compensation expense recognized by classification included in the consolidated statements of operations and comprehensive loss was as follows:

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Research and development	$ 11,965	$ 8,029	$ 3,994
Selling, general and administrative	9,823	9,439	6,699
Total	**$ 21,788**	**$ 17,468**	**$ 10,693**

Share-based compensation expense recognized by award type was as follows:

	Year ended December 31,		
	2020	2019	2018
		(in thousands)	
Award type			
Share options	$ 11,434	$ 7,896	$ 4,766
Restricted share units	7,364	4,117	3,020
Performance share units	2,990	5,455	2,907
Total	**$ 21,788**	**$ 17,468**	**$ 10,693**

As of December 31, 2020, the unrecognized compensation cost related to unvested awards under the various share-based compensation plans were:

	Unrecognized share-based compensation expense	Weighted average remaining period for recognition
	(in thousands)	(in years)
Award type		
Share options	$ 23,492	2.78
Restricted share units	14,489	2.09
Performance share units	1,763	1.03
Total	**$ 39,744**	**2.45**

The Company satisfies the exercise of share options and vesting of Restricted Share Units ("RSUs") and Performance Share Units ("PSUs") through newly issued shares.

The Company's share-based compensation plans include the 2014 Amended and Restated Share Option Plan (the "2014 Plan") and inducement grants under Rule 5653(c)(4) of The Nasdaq Global Select Market with terms similar to the 2014 Plan (together the "2014 Plans"). The Company previously had a 2012 Equity Incentive Plan (the "2012 Plan"). As of December 31, 2020, 14,000 fully vested share options are outstanding (December 31, 2019: 14,000) under the 2012 Plan.

At the general meeting of shareholders on January 9, 2014, the Company's shareholders approved the adoption of the 2014 Plan. At the annual general meetings of shareholders in June 2015, 2016 and 2018, uniQure shareholders approved amendments of the 2014 Plan, increasing the shares authorized for issuance by 1,070,000 shares in 2015, 3,000,000 in 2016 and 3,000,000 shares in 2018, for a total of 8,601,471 shares.

Share options

Share options are priced on the date of grant and, except for certain grants made to non-executive directors, vest over a period of four years. The first 25% vests after one year from the initial grant date and the remainder vests in equal quarterly installments over years two, three and four. Certain grants to non-executive directors vest in full after one year. Any options that vest must be exercised by the tenth anniversary of the initial grant date.

2014 Plan

The following tables summarize option activity under the Company's 2014 Plans for the year ended December 31, 2019:

	Options			
	Number of ordinary shares	Weighted average exercise price	Weighted average remaining contractual life in years	Aggregate intrinsic value (in thousands)
Outstanding at December 31, 2019	**2,683,104**	**$ 21.29**	**7.46**	**$ 135,238**
Granted	653,852	$ 49.63		
Forfeited	(172,548)	$ 42.03		
Expired	(6,451)	$ 45.76		
Exercised	(498,678)	$ 14.43		
Outstanding at December 31, 2020	**2,659,279**	**$ 28.13**	**7.18**	**32,729**
Thereof, fully vested and exercisable at December 31, 2020	1,542,405	$ 18.05	6.15	29,161
Thereof, outstanding and expected to vest after December 31, 2020	1,116,874	$ 42.06	8.61	3,568
Outstanding and expected to vest at December 31, 2019	1,346,337	$ 28.76		

Total weighted average grant date fair value of options issued during the period (in $ millions)		$	18.4
Granted to directors and officers during the period (options, grant date fair value $ in millions)	209,254	$	5.7
Proceeds from option sales during the period (in $ millions)		$	7.2

The following table summarizes information about the weighted average grant-date fair value of options during the years ended December 31:

	Options	Weighted average grant-date fair value
Granted, 2020	653,852	$ 28.08
Granted, 2019	647,526	23.57
Granted, 2018	937,832	15.90
Vested, 2020	713,924	14.04
Forfeited, 2020	(172,548)	24.63

The following table summarizes information about the weighted average grant-date fair value of options at December 31:

	Options	Weighted average grant-date fair value
Outstanding and expected to vest, 2020	1,116,874	$ 24.25
Outstanding and expected to vest, 2019	1,346,337	17.05

The fair value of each option issued is estimated at the respective grant date using the Hull & White option pricing model with the following weighted-average assumptions:

	Year ended December 31,		
Assumptions	**2020**	**2019**	**2018**
Expected volatility	70%	70% - 75%	75% - 80%
Expected terms	10 years	10 years	10 years
Risk free interest rate	0.76% - 1.44%	1.92% - 2.87%	2.67% - 3.20%
Expected dividend yield	0%	0%	0%

The Hull & White option model captures early exercises by assuming that the likelihood of exercises will increase when the share price reaches defined multiples of the strike price. This analysis is performed over the full contractual term.

The following table summarizes information about options exercised during the years ended December 31:

	Exercised during the year	Intrinsic value (in thousands)
2020	498,678	$ 11,927
2019	434,665	17,700
2018	388,203	7,515

Restricted Share Units

The following table summarizes the RSU activity for the year ended December 31, 2020:

	RSU	
	Number of ordinary shares	Weighted average grant-date fair value
Non-vested at December 31, 2019	**370,830**	**$ 28.62**
Granted	376,799	$ 48.18
Vested	(206,881)	$ 24.18
Forfeited	(73,404)	$ 46.41
Non-vested at December 31, 2020	**467,344**	**$ 43.56**
Total weighted average grant date fair value of RSUs granted during the period (in $ millions)		$ 18.2
Granted to directors and officers during the period (shares, $ in millions)	158,623	$ 7.4

The following table summarizes information about the weighted average grant-date fair value of RSUs granted during the years ended December 31:

	Granted during the year	Weighted average grant-date fair value
2020	376,799	$ 48.18
2019	198,504	38.63
2018	262,599	23.61

The following table summarizes information about the total fair value of RSUs that vested during the years ended December 31:

	Total fair value (in thousands)
2020	$ 12,156
2019	10,152
2018	8,546

RSUs generally vest over one to three years. RSUs granted to non-executive directors will vest one year from the date of grant.

Performance Share Units

The following table summarizes the PSU activity for the year ended December 31, 2020:

	PSU	
	Number of ordinary shares	Weighted average grant-date fair value
Non-vested at December 31, 2019	**479,422**	**$ 21.17**
Granted	91,003	$ 57.56
Vested	(354,105)	$ 17.44
Forfeited	(3,706)	$ 57.56
Non-vested at December 31, 2020	**212,614**	**$ 42.32**
Total weighted average grant date fair value of PSUs granted during the period (in $ millions)		$ 5.2

In January 2019, the Company awarded PSUs to its executives and other members of senior management. These PSUs were earned in January 2020 based on the Board's assessment of the level of achievement of agreed upon performance targets through December 31, 2019. The PSUs awarded for the year ended December 31, 2019 will vest on the third anniversary of the grant, subject to the grantee's continued employment.

The following table summarizes information about the weighted average grant-date fair value, determined at of the date these were earned, of PSUs granted during the years ended December 31:

	Granted during the year	Weighted average grant-date fair value
2020	91,003	$ 57.56
2019	132,362	$ 31.71
2018	—	$ —

The following table summarizes information about the total fair value of PSUs that vested during the years ended December 31:

	Total fair value (in thousands)
2020	$ 21,852
2019	1,056
2018	1,350

Employee Share Purchase Plan ("ESPP")

In June 2018, the Company's shareholders adopted and approved an ESPP allowing the Company to issue up to 150,000 ordinary shares. The ESPP is intended to qualify under Section 423 of the Internal Revenue Code of 1986. Under the ESPP, employees are eligible to purchase ordinary shares through payroll deductions, subject to any plan limitations. The purchase price of the shares on each purchase date is equal to 85% of the lower of the closing market price on the offering date or the closing market price on the purchase date of each three-month offering period. During the year ended December 31, 2020, 6,181 shares have been issued (December 31, 2019: 9,202 and December 31, 2018: 2,591). As of December 31, 2020, a total of 132,026 ordinary shares remains available for issuance under the ESPP plan.

12. Expenses by nature

Operating expenses excluding expenses presented in other expenses included the following expenses by nature:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Employee-related expenses	$ 75,926	$ 59,130	$ 46,254
Laboratory and development expenses	35,977	30,130	23,596
Office and housing expenses	13,388	10,588	7,281
Legal and advisory expenses	17,370	11,297	7,748
Depreciation, amortization, and impairment expenses	10,648	6,669	12,415
Patent and license expenses	2,899	1,654	1,202
Other operating expenses	8,772	8,813	1,618
Total	**$ 164,980**	**$ 128,281**	**$ 100,114**

Details of employee-related expenses for the years ended December 31 are as follows:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Wages and salaries	$ 40,919	$ 32,029	$ 26,646
Share-based compensation expenses	21,831	17,533	10,708
Consultant expenses	2,423	2,464	2,974
Social security costs	4,068	2,727	2,231
Health insurance	2,271	1,933	1,471
Pension costs - defined contribution plans	1,779	1,052	907
Other employee expenses	2,635	1,392	1,317
Total	**$ 75,926**	**$ 59,130**	**$ 46,254**

13. Other non-operating income / (expense)

Other non-operating income / (expense) consists of changes in the fair value of derivative financial instruments (see Note 4, “Fair value measurement”).

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Other non-operating income:			
Derivative gains	$ 483	$ —	$ 208
Total other non-operating income:	483	—	208
Other non-operating expense:			
Derivative losses	—	(2,530)	—
Total other non-operating expense:	—	(2,530)	—
Other non-operating income / (expense), net	**$ 483**	**$ (2,530)**	**$ 208**

The Company recorded a net gain of $0.5 million for the year ended December 31, 2020, compared to a net loss of $2.3 million and a net gain of $0.5 million for the years ended December 31, 2019 and December 31, 2018, respectively, related to the derivative financial instruments issued as part of its collaboration with BMS. The $0.5 million gain for the year ended December 31, 2020 includes a $2.3 million gain related to the reduction of the fair market value of the BMS warrants, a $0.8 million gain related to the derecognition of the BMS warrants on December 1, 2020 and a $2.6 million loss related to the initial recognition of the derivative financial liability related to the CoC-payment. The Company recorded a net loss of $0.2 million and $0.3 million for the years ended December 31, 2019 and December 31, 2018, respectively, related to warrants issued to Hercules.

14. Income taxes

a. Income tax benefit / (expense)

No current tax expense or liabilities were recorded in 2020 by the Company's Dutch and U.S entities. Due to the uncertainty surrounding the realization of favorable tax attributes in future tax returns, the Company has recorded a full valuation allowance against the Company's net deferred tax assets in the Netherlands. The Company released the full valuation allowance against the Company's net deferred tax assets in the United States as of December 31, 2020.

There are no significant unrecognized tax benefits as of December 31, 2020 and 2019.

For the years ended December 31, 2020, 2019 and 2018, loss before income taxes consists of the following:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Dutch operations	$ (130,493)	$ (111,820)	$ (85,721)
U.S. operations	(10,950)	(12,381)	2,646
Foreign operations	—	—	3
Total	**$ (141,443)**	**$ (124,201)**	**$ (83,073)**

The income tax benefit / (expense) for the years ended December 31, 2020, 2019 and 2018, consists of the following:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Current tax expense			
Dutch operations	$ —	$ —	$ —
U.S. operations	—	—	—
Foreign operations	—	—	(22)
Total current tax expense	$ —	$ —	$ (22)
Deferred tax benefit / (expense)			
Dutch operations	$ —	$ —	$ (209)
U.S. operations	16,419	—	—
Foreign operations	—	—	—
Total deferred tax benefit / (expense)	$ 16,419	$ —	$ (209)
Total income tax benefit / (expense)	**$ 16,419**	**$ —**	**$ (231)**

b. Tax rate reconciliation

The reconciliation of the amount of income tax benefit / (expense) that would result from applying the Dutch statutory income tax rate to the Company's reported amount of income tax benefit / (expense) for the years ended December 31, 2020, 2019 and 2018, is as follows:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
Loss before income tax income / (expense) for the period	$ (141,443)	$ (124,201)	$ (83,073)
Expected income tax benefit at the tax rate enacted in the Netherlands (25%)	35,361	31,050	20,768
Difference in tax rates between the Netherlands and the U.S. as well as other foreign countries	247	(495)	(106)
Release of valuation allowance related to expected future taxable income of U.S. operations	16,419	—	—
Other net change in valuation allowance	(30,568)	(25,583)	(19,207)
Nondeductible expenses	(5,041)	(4,972)	(2,648)
Change in fair value of contingent consideration	—	—	962
Income tax benefit / (expense)	**$ 16,419**	**$ —**	**$ (231)**

Nondeductible expenses predominantly relate to share-based compensation expenses and affected the effective tax rate by an amount of $5.8 million in 2020 (2019: $4.4 million; 2018: $2.7 million). Derivative financial instruments affected the effective tax rate by income of $0.8 million in 2020 (expense of $0.6 million in 2019; $0.0 million in 2018), which reduced the nondeductible expenses resulting from share-based compensation expenses.

c. Significant components of deferred taxes

The tax effects of temporary differences and carryforwards that give rise to significant portions of deferred tax assets and deferred tax liabilities at December 31, 2020 and 2019 are as follows:

	Years ended December 31,	
	2020	2019
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 158,614	$ 99,644
Lease liabilities	9,515	7,861
Intangible assets	1,702	770
Interest carryforwards	1,597	—
Accrued expenses and other current liabilities	1,118	628
Property, plant and equipment	1,072	761
Derivative financial instrument	661	-
Deferred revenue	—	6,676
Gross deferred tax asset	**$ 174,279**	**$ 116,340**
Less valuation allowance	(150,113)	(109,856)
Net deferred tax asset	**$ 24,166**	**$ 6,484**
Right-of-use asset	(7,702)	(6,484)
Prepaid expenses	(45)	—
Deferred tax liability	**$ (7,747)**	**$ (6,484)**
Net deferred tax asset	**$ 16,419**	**$ —**

Changes in the valuation allowance were as follows:

	Years ended December 31,		
	2020	2019	2018
		(in thousands)	
January 1,	$ 109,856	$ 85,100	$ 93,682
Changes related to reduction of deferred revenue recorded in equity upon implementation of ASC 606 Revenue recognition as of January 1, 2018	—	—	(6,229)
Changes recorded in profit and loss	30,568	25,583	19,207
Increase/(reduction) related to 2020, 2019 and 2018 Dutch tax reforms	18,287	4,059	(15,670)
Release of valuation allowance related to expected current year and future periods recorded in profit and loss	(16,419)	—	—
Other changes including currency translation effects	7,821	(4,886)	(5,890)
December 31,	**$ 150,113**	**$ 109,856**	**$ 85,100**

Included within changes recorded in profit and loss for the year ended December 31, 2020 are benefits of $1.2 million from the utilization of U.S. net operating loss carryforwards ($0.8 million for the year ended December 31, 2019 and $0.9 million for the year ended December 31, 2018).

The valuation allowance as of December 31, 2020 is primarily related to net operating loss carryforwards in the Netherlands that, in the judgment of management, are not more-likely than-not to be realized. In addition, the valuation allowance as of December 31, 2019 included deferred tax assets for net operating loss carryforwards and temporary differences in the United States of America. Management considered projected future taxable income and tax-planning strategies in making this assessment. A valuation allowance will be recorded against deferred tax assets if it is more likely than not that some or all the deferred tax assets will not be realized.

Netherlands

The Company determined that in accordance with Dutch tax law it would recognize the CSL Behring License Revenue as well as the License Fees as taxable results as of the date on which the Company is contractually entitled to receive (or obligated to make) a payment under the CSL Behring Agreement. The Company expects to continue to incur taxable losses in the Netherlands except for the period in which it would receive the $450.0 million upfront payment under the CSL Behring Agreement. In the event that the Company recognizes the $450.0 million upfront payment in 2021, such payment is expected to be subject to Dutch corporate income tax at a rate of 25.0%. However, the Company does not expect that it will be required to pay any income taxes in the period in which it recognizes the $450.0 million upfront payment as taxable revenue, as such payment is not expected to exceed the net operating losses that it carries forward in the Netherlands. The Company specifically assessed the impact of the CSL Behring agreement with respect to retaining a full valuation allowance as of December 31, 2020. Closing of the CSL Behring Agreement is contingent on the successful completion of reviews under the antitrust laws in the United States, Australia, and the United Kingdom. The transactions have not closed as of December 31, 2020 as the Company received a Second Request from the United States Federal Trade Commission, on January 4, 2021. Closing of the transaction is dependent on the timing, extent, and result of the Second Request. In its assessment of whether or not it was more likely than not that the Company's deferred tax assets in the Netherlands will be realized, the Company considered all relevant facts and circumstances, including similar regulatory reviews as well as the five-year cumulative losses reported by the Company in the Netherlands. The Company concluded that it should continue to record a full valuation allowance as of December 31, 2020 in relation to its Dutch net operating loss carryforwards.

A portion of the valuation allowance for deferred tax assets relates to follow-on offering costs. Any subsequently recognized tax benefits will be credited directly to contributed capital. As of December 31, 2020, that amount was $7.7 million ($6.9 million as of December 31, 2019). The change is attributable to changes in the foreign currency rate.

The Dutch corporate tax rate for fiscal years 2018, 2019 and 2020 was 25%. During the years 2018 and 2019, the Dutch government enacted various changes to the corporate income tax rate applicable to future fiscal years. In September 2020, further changes were enacted that retain the corporate rate at 25% from 2021 onwards.

A tax reform in December 2018 limited the carryforward of tax losses arising from January 1, 2019, to six years after the end of the respective period. Tax losses incurred prior to this date continue to expire nine years after the end of the respective period.

As of December 31, 2020, new loss compensation rules were accepted by the Dutch Senate. However, the bill includes a provision that the new compensation rules will be effective by a separate Governmental Decree, which has not been introduced as of December 31, 2020. Hence, the new loss compensation rules are not enacted as of December 31, 2020. If enacted, the rules allow losses to be carried forward indefinitely, but from fiscal year 2022 onwards would limit offsetting taxable profit in excess of EUR 1.0 million to 50% of the taxable profit.

The Dutch fiscal unity as of December 31, 2020 has an estimated $588.2 million (2019: $414.0 million; 2018: $311.7 million) of taxable losses that can be offset in the following six to seven years. The expiration dates of these Dutch losses are summarized in the following table. In the year ended December 31, 2020 unused tax losses of $18.5 million (December 31, 2019: $20.7 million) expired.

	2021	2022	2023	2024	2025-2027
			(in thousands)		
Loss expiring	$ 15,206	$ 25,878	$ 25,202	$ —	$ 521,931

The fiscal periods after 2017 are still open for inspection by the Dutch tax authorities.

United States of America

The federal corporate tax rate in the U.S. is 21%. In addition, the Company is subject to state taxes resulting in a combined tax rate of 27.32% for its U.S. operation. As of December 31, 2020, an estimated $42.3 million of net operating losses remain to be carried forward. These losses will expire between 2035 and 2037.

The Company's U.S. operations generated taxable income in the fiscal years 2018, 2019 and 2020. Based on the current design of the Company's worldwide operations, the Company expects to continue to generate taxable income in the U.S. during the foreseeable future. As of December 31, 2020, the Company considers it more likely than not that it will utilize its net deferred tax assets in the U.S. and therefore released the remaining valuation allowance of $16.4 million through profit and loss as of this date.

Under the provision of the Internal Revenue Code, the U.S. net operating losses may become subject to an annual limitation in the event of certain cumulative exchange in the ownership interest of significant shareholders over a three-year period in excess of 50 percent, as defined under Section 382 and 383 of the Internal Revenue Code. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation.

The fiscal periods after 2017 are still open for inspection by the Internal Revenue Service. The Company is currently not under examination by the IRS for any tax years.

15. Basic and diluted earnings per share

Diluted earnings per share is calculated by adjusting the weighted average number of ordinary shares outstanding, assuming conversion of all potentially dilutive ordinary shares. As the Company has incurred a loss in the years presented, all potentially dilutive ordinary shares would have an antidilutive effect, if converted, and thus have been excluded from the computation of loss per share. The shares are presented without giving effect to the application of the treasury method or exercise prices that would be above the share price as of December 31, 2020, December 31, 2019, and December 31, 2018, respectively. In addition, the BMS warrants were not exercisable as of December 31, 2019, and December 31, 2018, since this would have required the prior designation of Collaboration Targets by BMS. This would generally have resulted in a lower number of potentially dilutive ordinary shares as some stock option grants as well as the BMS warrants would have been excluded.

The potentially dilutive ordinary shares are summarized below:

	Years ended December 31,		
	2020	2019	2018
	(ordinary shares)		
BMS warrants (derecognized as of December 1, 2020 - see Note 4, "Fair value measurement")	—	8,893,000	8,575,000
Stock options under 2014 Plans	2,659,279	2,683,104	2,673,712
Non-vested RSUs and earned PSUs	679,958	850,252	789,490
Stock options under previous option plan	14,000	14,000	32,567
Hercules warrants (exercised February 1, 2019)	—	—	37,175
Employee share purchase plan	560	485	1,012
Total potential dilutive ordinary shares	**3,353,797**	**12,440,841**	**12,108,956**

16. Commitments and contingencies

In the course of its business, the Company enters as a licensee into contracts with other parties regarding the development and marketing of its pipeline products. Among other payment obligations, the Company is obligated to pay royalties to the licensors based on future sales levels and milestone payments whenever specified development, regulatory and commercial milestones are met. As both future sales levels and the timing and achievement of milestones are uncertain, the financial effect of these agreements cannot be estimated reliably.

17. Related party transaction

Between June 2015 and December 2020, BMS was considered a related party due to the combination of its equity investment in the Company (December 31, 2020: 2.4 million ordinary shares or 5.3% of outstanding ordinary shares), the warrants as well as the potential obligations arising from the expansion of collaboration targets. On December 1, 2020, the Company entered into the amended BMS CLA. All transactions subsequent to the effective date of the amended BMS CLA are considered to no longer be with a related party due to the elimination of the potential obligations related to additional Collaboration Targets (see Note 3 "Collaboration arrangements and concentration of credit risk") as well as the elimination of the BMS warrants (see Note 4, "Fair value measurement").

On September 14, 2020, the Company appointed Ricardo Dolmetsch, Ph.D. as President, Research and Development. Dr. Dolmetsch succeeded Sander van Deventer, M.D., Ph.D., the former Executive Vice President, Research and Product Development. On August 25, 2020, the Company entered into a separation agreement with Robert Gut, M.D., Ph.D., pursuant to which Dr. Gut transitioned from his role as Chief Medical Officer on October 14, 2020, to be appointed a non-executive director of the Board of Directors. On December 1, 2020, at an extraordinary general meeting, the Company's shareholders voted to approve the appointment of Dr. Gut as a non-executive director on the Board of Directors. Dr. Gut had previously been appointed as a non-executive director on the Board of Directors on June 13, 2018 by the Company's shareholders and had resigned as a non-executive director on August 20, 2018, to be appointed as the Company's Chief Medical Officer. On October 24, 2018, at an extraordinary general meeting, the Company's shareholders voted to approve the appointment of Dr. Gut as an executive director on the Board of Directors.

On June 17, 2020, the Company's shareholders voted to approve the appointment of Leonard E. Post, Ph.D., as a non-executive director of the Board of Directors. Dr. Post replaced Dr. David Schaffer, whose term as a non-executive director of the Board of Directors ended on the same date. Dr. Post has also assumed the role of chair of the Company's Research and Development Committee of the Board of Directors.

On August 20, 2019, the Company promoted Alex Kuta, Ph.D., to Executive Vice President, Operations. Dr. Kuta, in addition to regulatory affairs, became responsible for global quality as well as GMP manufacturing at the Company's facility in Lexington, Massachusetts. As of the same date Sander van Deventer, M.D., Ph.D., was promoted to Executive Vice President, Research and Product Development, and Dr. van Deventer, in addition to his responsibilities for research, also became responsible for the Company's product development. As a result of these changes Scott McMillan, Ph.D. retired from uniQure. The employment of Dr. van Deventer terminated on September 14, 2020.

In August 2019, the Company entered into an Amended and Restated Agreement Collaboration and License Agreement ("Amended CLA") as well as an additional new Collaboration and License Agreement ("New CLA") with its related party 4DMT Molecular Therapeutics, Inc. ("4DMT"). In the Amended CLA, the Company received from 4DMT an exclusive, sublicensable, worldwide license under certain 4DMT intellectual property rights to research, develop, make, use, and commercialize previously selected Adeno-associated virus ("AAV") capsid variants and certain associated products using 4DMT proprietary AAV technology for delivery of gene therapy constructs to cells in the central nervous system and the liver ("the Field"). In the New CLA, the parties agreed to research and develop, at 4DMT's cost, new AAV capsid variants using 4DMT proprietary AAV technology for delivery of up to six additional transgene constructs in the Field that will be selected by the Company. As of June 2020, 4DMT is no longer considered a related party as a result of David Schaffer no longer being a non-executive member of the Company's Board of Directors.

18. Subsequent events

Amendment Loan Facility

As of December 31, 2020, a $35.0 million term loan was outstanding in accordance with the 2018 Amended Facility between the Company and Hercules.

On January 29, 2021, the Company and Hercules amended the Company's loan facility with Hercules Capital Inc. entered, ("2021 Amended Facility"). Pursuant to the 2021 Amended Facility, Hercules agreed to the 2021 Term Loan, increasing the aggregate principal amount of the term loan facility from $35.0 million to $135.0 million. On January 29, 2021, the Company drew down $35.0 million of the 2021 Term Loan. The Company may draw down the remaining $65.0 million under the 2021 Term Loan in a series of one or more advances of not less than $20.0 million each until December 15, 2021. Advances under the 2021 Term Loan bear interest at a rate equal to the greater of (i) 8.25% or (ii) 8.25% plus the prime rate, less 3.25% per annum. The principal balance and all accrued but unpaid interest on advances under 2021 Term Loan is due on June 1, 2023, which date may be extended by the Company by up to two twelve-month periods. Advances under the 2021 Term Loan may not be prepaid until six months after the Closing Date, following which the Company may prepay all such advances without charge.

In addition to the 2021 Term Loan, the amendment also extends the interest-only payment period of the previously funded $35.0 million term loan from January 1, 2022 to June 1, 2023.

The Company paid a $0.4 million facility charge on January 29, 2021. End of term charges in respect of advances under the 2021 Term Loan range from 1.65% to 6.85% depending on the maturity date.

EXHIBIT INDEX

Exhibit No.	Description
3.1	Amended Articles of Association of the Company (incorporated by reference to Exhibit 3.1 of the Company's annual report on Form 10-K for the year ended December 31, 2018 (file no. 0001-36294) filed with the Securities and Exchange Commission).
4.1*	Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934.
10.1t	2014 Share Incentive Plan (incorporated by reference to Exhibit 4.3 of the Company's registration statement on Form S-8 (file no. 333-225629) filed with the Securities and Exchange Commission).
10.2t	Form of Inducement Share Option Agreement under 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.2 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
10.3t	Form of Share Option Agreement under 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.3 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
10.4t	Form of Restricted Stock Unit Award under the 2014 Share Incentive (incorporated by reference to Exhibit 10.4 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2017 filed with the Securities and Exchange Commission).
10.5t	Form of Performance Stock Unit Award under the 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.5 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2017 filed with the Securities and Exchange Commission).
10.6t	Employment Agreement dated December 9, 2014 between uniQure, Inc. and Matthew Kapusta (incorporated by reference to Exhibit 10.6 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
10.7t	Amendment to the Employment Agreement between uniQure, Inc. and Matthew Kapusta, dated March 14, 2017 (incorporated by reference to Exhibit 10.7 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
10.8t	Amendment to the Employment Agreement between uniQure, Inc. and Matthew Kapusta, dated October 26, 2017 (incorporated by reference to Exhibit 10.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 31, 2017 filed with the Securities and Exchange Commission).
10.10	Patent License Agreement (L-107-2007), effective as of May 2, 2007, by and between the Company and the National Institutes of Health, as amended on December 31, 2009, May 31, 2013, and November 11, 2013 (incorporated by reference to Exhibit 10.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on March 31, 2017 filed with the Securities and Exchange Commission).
10.11	Patent License Agreement (L-116-2011), effective as of August 10, 2011, by and between the Company and National Institutes of Health, as amended on May 31, 2013 and November 11, 2013 (incorporated by reference to Exhibit 10.2 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on March 31, 2017 filed with the Securities and Exchange Commission).
10.18	Lease relating to 113 Hartwell Avenue, Lexington, Massachusetts, dated as of July 24, 2013, by and between the Company and King113 Hartwell LLC (incorporated by reference to Exhibit 10.28 of the Company's registration statement on Form F-1 (file no. 333-193158) filed with the Securities and Exchange Commission).
10.19	Business Acquisition Agreement, dated as of February 16, 2012, by and among Amsterdam Molecular Therapeutics (AMT) Holding N.V., the Company and the other Parties listed therein (incorporated by reference to Exhibit 10.29 of the Company's registration statement on Form F-1 (file no. 333-193158) filed with the Securities and Exchange Commission).

10.20	Deed of Assignment of Certain Assets and Liabilities of Amsterdam Molecular Therapeutics (AMT) Holding N.V., dated as of April 5, 2012, by and among Amsterdam Molecular Therapeutics (AMT) Holding B.V., Amsterdam Molecular Therapeutics (AMT) Holding IP B.V. and Amsterdam Molecular Therapeutics (AMT) Holding N.V. (incorporated by reference to Exhibit 10.30 of the Company's registration statement on Form F-1 (file no. 333-193158) filed with the Securities and Exchange Commission).
10.21	Agreement for Transfer of Certain Assets and Liabilities of Amsterdam Molecular Therapeutics (AMT) Holding N.V., dated as of February 16, 2012, by and among Amsterdam Molecular Therapeutics (AMT) Holding B.V., Amsterdam Molecular Therapeutics (AMT) Holding IP B.V. and Amsterdam Molecular Therapeutics (AMT) Holding N.V. (incorporated by reference to Exhibit 10.31 of the Company's registration statement on Form F-1 (file no. 333-193158) filed with the Securities and Exchange Commission).
10.26	Second Amended and Restated Loan and Security Agreement, dated as of May 6, 2016 by and among uniQure Biopharma B.V., uniQure, Inc., uniQure IP B.V., the Company's subsidiaries listed therein, and Hercules Technology Growth Capital, Inc (incorporated by reference to Exhibit 10.30 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission.
10.27†	Collaboration and License Agreement by and between uniQure Biopharma B.V. and Bristol-Myers Squibb Company dated April 6, 2015 (incorporated by reference to Exhibit 4.30 of the Company's annual report on Form 20-F (file no. 001-36294) filed with the Securities and Exchange Commission).
10.29†	Investor Agreement by and between uniQure Biopharma B.V. and Bristol-Myers Squibb Company dated April 6, 2015 (incorporated by reference to Exhibit 4.32 of the Company's annual report on Form 20-F (file no. 001-36294) filed with the Securities and Exchange Commission).
10.32	Lease relating to Paasheuvelweg 25, dated as of March 7, 2016, by and between 52 IFH GmbH & Co. KG and uniQure biopharma B.V. (incorporated by reference to Exhibit 10.36 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
10.34t	Employment Agreement dated August 4, 2017 between uniQure biopharma B.V. and Sander van Deventer (incorporated by reference to Exhibit 10.2 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2017 filed with the Securities and Exchange Commission).
10.36t	Employment Agreement dated July 15, 2017 between uniQure biopharma B.V. and Christian Klemt (incorporated by reference to Exhibit 10.4 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2017 filed with the Securities and Exchange Commission).
10.37†	Assignment and License Agreement dated April 17, 2017 between Professor Paolo Simioni and uniQure biopharma B.V. (incorporated by reference to Exhibit 10.1 of the Company's periodic report on Form 8-K (file no. 001-36294) filed on October 19, 2017 with the Securities and Exchange Commission).
10.38t	Employment Agreement dated August 20, 2018 by and between uniQure, Inc. and Dr. Robert Gut (incorporated by reference to Exhibit 10.38 of the Company's annual report on Form 10-K for the year ended December 31, 2018 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.39	Amendment No. 1 to Second Amended and Restated Loan and Security Agreement dates as of December 6, 2018 by and among uniQure Biopharma B.V., uniQure, Inc., uniQure IP B.V., the Company, and Hercules Technology Growth Capital, Inc (incorporated by reference to Exhibit 10.1 of the Company's current report on Form 8-K (file no. 001-36294) filed with the Securities and Exchange Commission) filed on December 10, 2018.
10.40	First Amendment Lease relating to 113 Hartwell Avenue, Lexington, Massachusetts, dated as of July 24, 2013, by and between the Company and King113 Hartwell LLC (incorporated by reference to Exhibit 10.1 of the Company's current report on form 8-K (file no. 001-36294) filed with the Securities and Exchange Commission) filed on November 15, 2018.
10.41t	Employee Share Purchase Plan (incorporated by reference to Exhibit 4.2 of the Company's registration statement on Form S-8 (file no. 333-225629) filed with the Securities and Exchange Commission) filed on June 14, 2018.

10.42	Second Amendment Lease relating to 113 Hartwell Avenue, Lexington Massachusetts, dated as of June 17, 2019, by and between the Company and King 113 Hartwell LLC (incorporated by reference to Exhibit 10.42 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2019 filed with the Securities and Exchange Commission).
10.43	Form of Share Option Agreement, effective June 18, 2019, under the 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.43 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2019 filed with the Securities and Exchange Commission).
10.44t	Amended and Restated Employment Agreement, executed September 17, 2019, by and between the Company and Dr. Kuta (incorporated by reference to Exhibit 10.1 of the Company's current report on Form 8-K (file no. 001-36294) filed with the Securities and Exchange Commission) filed on September 20, 2019.
10.45t	Employment Agreement, executed September 17, 2019, by and between the Company and Dr. Sander van Deventer (incorporated by reference to Exhibit 10.2 of the Company's current report on form 8-K (file no. 001-36294) filed with the Securities and Exchange Commission) filed on September 20, 2019.
10.47	Amended and Restated Collaboration and License Agreement by and between 4D Molecular Therapeutics, Inc and uniQure biopharma B.V., dated August 6, 2019 (incorporated by reference to Exhibit 10.4 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 30, 2019 filed with the Securities and Exchange Commission).
10.48	Collaboration and License Agreement by and between 4D Molecular Therapeutics, Inc and uniQure biopharma B.V., dates August 6, 2019 (incorporated by reference to Exhibit 10.5 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 30, 2019 filed with the Securities and Exchange Commission).
10.49t	Amended and Restated Employment Agreement, executed March 1, 2020 by and between uniQure biopharma B.V. and Christian Klemt (incorporated by reference to Exhibit 10.49 of the Company's annual report on Form 10-K for the year ended December 31, 2019 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.50t	Amended and Restated Employment Agreement, executed March 1, 2020 by and between uniQure Inc. and Dr. Robert Gut (incorporated by reference to Exhibit 10.50 of the Company's annual report on Form 10-K for the year ended December 31, 2019 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.51t	Amended and Restated Employment Agreement, executed March 1, 2020 by and between uniQure Inc. and Maria Cantor (incorporated by reference to Exhibit 10.51 of the Company's annual report on Form 10-K for the year ended December 31, 2019 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.52t	Amended and Restated Employment Agreement, executed March 1, 2020 by and between uniQure Inc. and Jonathan Garen (incorporated by reference to Exhibit 10.52 of the Company's annual report on Form 10-K for the year ended December 31, 2019 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.53†	Commercialization and License Agreement by and between uniQure biopharma B.V. and CSL Behring LLC dated June 24, 2020 (incorporated by reference to Exhibit 10.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2020 filed with the Securities and Exchange Commission).
10.54t	Separation agreement, executed August 25, 2020, by and between uniQure biopharma B.V. and Sander van Deventer (incorporated by reference to Exhibit 10.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 30, 2020 filed with the Securities and Exchange Commission).
10.55t	Separation agreement, executed August 25, 2020, by and between uniQure Inc. and Robert Gut (incorporated by reference to Exhibit 10.2 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 30, 2020 filed with the Securities and Exchange Commission).
10.56t	Employment agreement, executed September 14, 2020, by and between uniQure Inc. and Ricardo Dolmetsch (incorporated by reference to Exhibit 10.3 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on September 30, 2020 filed with the Securities and Exchange Commission).

10.57*†	Amendment to Collaboration and License Agreement by and between uniQure Biopharma B.V. and Bristol-Myers Squibb Company dated December 1, 2020.
10.58*	Amendment No. 2 to Second Amended and Restated Loan and Security Agreement as of January 29, 2021 by and among uniQure Biopharma B.V., uniQure, Inc., uniQure IP B.V., the Company and Hercules Capital Inc.
14.1	Code of Ethics (incorporated by reference to Exhibit 14.1 of the Company's annual report on Form 10-K (file no. 001-36294) for the period ending December 31, 2016 filed with the Securities and Exchange Commission).
21.1*	Subsidiaries of the Company.
23.1*	Consent of Independent Registered Public Accounting Firm – KPMG Accountants N.V.
23.2*	Consent of Independent Registered Public Accounting Firm – PricewaterhouseCoopers Accountants N.V.
24.1*	Power of Attorney (incorporated by reference to the signature page of this Annual Report on Form 10-K).
31.1*	Rule 13a-14(a)/15d-14(a) Certification of Chief Executive Officer.
31.2*	Rule 13a-14(a)/15d-14(a) Certification of Chief Financial Officer.
32.1*	Section 1350 Certification.
101*	The following materials from the Company's Annual Report on Form 10-K for the year ended December 31, 2020, formatted in Inline XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Income (Loss), (iii) Consolidated Statements of Shareholders' Equity, (iv) Consolidated Statements of Cash Flows and (v) Notes to Consolidated Financial Statements.
104*	The cover page from the Company's Annual Report on Form 10-K for the year ended December 31, 2020, has been formatted in Inline XBRL.

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

* Filed herewith

t Indicates a management contract or compensatory plan or arrangement.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

UNIQURE, N.V.

By: /s/ MATTHEW KAPUSTA
Matthew Kapusta
Chief Executive Officer
(Principal Executive and Financial Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Matthew Kapusta and Christian Klemt, jointly and severally, his or her attorney-in-fact, with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ MATTHEW KAPUSTA Matthew Kapusta	Chief Executive Officer, Chief Financial Officer and Director (Principal Executive and Financial Officer)	March 1, 2021
/s/ CHRISTIAN KLEMT Christian Klemt	Chief Accounting Officer	March 1, 2021
/s/ PHILIP ASTLEY SPARKE Philip Astley Sparke	Director	March 1, 2021
/s/ MADHAVAN BALACHANDRAN Madhavan Balachandran	Director	March 1, 2021
/s/ ROBERT GUT Robert Gut	Director	March 1, 2021
/s/ JACK KAYE Jack Kaye	Director	March 1, 2021
/s/ DAVID MEEK David Meek	Director	March 1, 2021
/s/ LEONARD POST Leonard Post	Director	March 1, 2021
/s/ PAULA SOTEROPOULOS Paula Soteropoulos	Director	March 1, 2021
/s/ JEREMY P. SPRINGHORN Jeremy P. Springhorn	Director	March 1, 2021

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following description sets forth certain material terms and provisions of uniQure N.V.'s ("uniQure N.V.", "we," "us," and "our") securities that are registered under Section 12 of the Securities Exchange Act of 1934, as amended. The description below of our ordinary shares and provisions of our articles of association are summaries and are qualified by reference to our articles of association and the applicable provisions of Dutch law.

DESCRIPTION OF CAPITAL STOCK

The following description of the general terms and provisions of our ordinary shares is a summary only and therefore is not complete and is subject to, and qualified in its entirety by reference to, the terms and provisions of our articles of association. Our articles of association have been filed with the SEC as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.1 is a part and you should read the articles for provisions that may be important to you.

Authorized Ordinary Shares

Our articles of association provide an authorized share capital of 60,000,000 ordinary shares, each with a nominal value per share of €0.05.

Form of Ordinary Shares

We issue our ordinary shares in registered book-entry form and such shares are not certificated.

NASDAQ Global Market Listing

Our ordinary shares are listed on The NASDAQ Global Market under the symbol "QURE."

Comparison of Dutch corporate law and our Articles of Association and Delaware corporate law

The following comparison between Dutch corporate law, which applies to us, and Delaware corporate law, the law under which many publicly listed companies in the United States are incorporated, discusses additional matters not otherwise described in this exhibit. This summary is subject to Dutch law, including Book 2 of the Dutch Civil Code and Delaware corporation law, including the Delaware General Corporation Law.

Corporate governance

Duties of directors

The Netherlands. We have a one tier board structure consisting of our executive directors and non-executive directors. Under the one-tier board structure, both the executive and non-executive directors will be collectively responsible for the management performed by the one-tier board and for the general policy and strategy of a company. The executive directors are responsible for the day-to-day management of a company. The non-executive directors are responsible for supervising the conduct of, and providing advice to, the executive directors and for providing supervision with respect to the company's general state of affairs. Each executive director and non-executive director has a duty to act in the corporate interest of the company. Under Dutch law, the corporate interest extends to the interests of all corporate stakeholders, such as shareholders, creditors, employees, customers and suppliers. The duty to act in the corporate interest of the company also applies in the event of a proposed sale or split-up of a company, whereby the circumstances generally dictate how such duty is to be applied. Any resolution of the board regarding a significant change in the identity or character of a company requires shareholders' approval.

Delaware. The board of directors bears the ultimate responsibility for managing the business and affairs of a corporation. In discharging this function, directors of a Delaware corporation owe fiduciary duties of care and loyalty to the corporation and to its stockholders. Delaware courts have decided that the directors of a Delaware corporation are required to exercise informed business judgment in the performance of their duties. Informed business judgment means that the directors have informed themselves of all material information reasonably available to them. Delaware courts have also imposed a heightened standard of conduct upon directors of a Delaware corporation who take any action designed to defeat a threatened change in control of the corporation. In addition, under Delaware law, when the board of directors of a Delaware corporation approves the sale or break-up of a corporation, the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the stockholders.

Director terms

The Netherlands. Under Dutch law, executive directors of a listed company are generally appointed for a term of a maximum of four years and reappointed for a term of a maximum of four years at a time. Non-executive directors of a listed company are generally appointed for a term of a maximum of four years and reappointed once for another term of a maximum of four years. Non-executive directors of a listed company may subsequently be reappointed for a term of a maximum of two years, which reappointment may be extended by at most two years. Our executive and non-executive directors are, in principle, appointed by the general meeting of shareholders upon the binding nomination of the non-executive directors.

The general meeting of shareholders is entitled at all times to suspend or dismiss a director. The general meeting of shareholders may only adopt a resolution to suspend or dismiss such director by at least a two-thirds majority of the votes cast, if such majority represents more than half of the issued share capital of the company.

Delaware. The Delaware General Corporation Law generally provides for a one-year term for directors, but permits directorships to be divided into up to three classes with up to three-year terms, with the years for each class expiring in different years, if permitted by a company's certificate of incorporation, an initial bylaw or a bylaw adopted by the stockholders. A director elected to serve a term on such a classified board may not be removed by stockholders without cause. There is no limit in the number of terms a director may serve.

Director vacancies

The Netherlands. Under Dutch law, directors are appointed by the general meeting of shareholders. Under our articles of association, directors are, in principle, appointed by the general meeting of shareholders upon the binding nomination by the non-executive directors. However, the general meeting of shareholders may at all times overrule such binding nomination by a resolution adopted by at least a two-thirds majority of the votes cast, provided such majority represents more than half of the issued share capital of our company. If the general meeting of shareholders overrules the binding nomination, the non-executive directors must make a new nomination.

Delaware. The Delaware General Corporation Law provides that vacancies and newly created directorships may be filled by a majority of the directors then in office (even though less than a quorum) unless (1) otherwise provided in the certificate of incorporation or bylaws of the corporation or (2) the certificate of incorporation directs that a particular class of stock is to elect such director, in which case any other directors elected by such class, or a sole remaining director elected by such class, will fill such vacancy.

Conflict-of-interest transactions

The Netherlands. Pursuant to Dutch law and our articles of association, directors may not take part in any discussion or decision-making that involves a subject or transaction in relation to which they have a personal direct or indirect conflict of interest with us. Our articles of association provide that if as a result thereof, the board is unable to act the resolution will be adopted by the general meeting of shareholders.

Delaware. The Delaware General Corporation Law generally permits transactions involving a Delaware corporation and an interested director of that corporation if:

- the material facts as to the director's relationship or interest are disclosed and a majority of disinterested directors consent;
- the material facts are disclosed as to the director's relationship or interest and a majority of shares entitled to vote thereon consent; or
- the transaction is fair to the corporation at the time it is authorized by the board of directors, a committee of the board of directors or the stockholders.

Shareholder rights

Voting rights

The Netherlands. In accordance with Dutch law and our articles of association, each issued ordinary share confers the right to cast one vote at the general meeting of shareholders. Each holder of ordinary shares may cast as many votes as it holds shares. Shares that are held by us or our direct or indirect subsidiaries do not confer the right to vote. Dutch law does not permit cumulative voting for the election of executive directors and non-executive directors.

For each general meeting of shareholders, a record date will be applied with respect to ordinary shares in order to establish which shareholders are entitled to attend and vote at a specific general meeting of shareholders. Such record date is set by the board. The record date and the manner in which shareholders can register and exercise their rights will be set out in the convocation notice of the meeting.

Delaware. Under the Delaware General Corporation Law, each stockholder is entitled to one vote per share of stock, unless the certificate of incorporation provides otherwise. In addition, the certificate of incorporation may provide for cumulative voting at all elections of directors of the corporation, or at elections held under specified circumstances. Either the certificate of incorporation or the bylaws may specify the number of shares and/or the amount of other securities that must be represented at a meeting in order to constitute a quorum, but in no event will a quorum consist of less than one third of the shares entitled to vote at a meeting.

Stockholders as of the record date for the meeting are entitled to vote at the meeting, and the board of directors may fix a record date that is no more than 60 nor less than ten days before the date of the meeting, and if no record date is set then the record date is the close of business on the day next preceding the day on which notice is given, or if notice is waived then the record date is the close of business on the day next preceding the day on which the meeting is held. The determination of the stockholders of record entitled to notice or to vote at a meeting of stockholders shall apply to any adjournment of the meeting, but the board of directors may fix a new record date for the adjourned meeting.

Shareholder proposals

The Netherlands. Pursuant to our articles of association, extraordinary general meetings of shareholders will be convened by the board or by those who are authorized by law or pursuant to our articles of association to do so. Pursuant to Dutch law, one or more shareholders representing at least one-tenth of the issued share capital of the company may request the Dutch courts to order that they be authorized by the court to convene a general meeting of shareholders. The court shall disallow the request if it does not appear that the applicants have previously requested the board to convene a general meeting of shareholders and the board has taken the necessary steps so that the general meeting of shareholders could be held within six weeks after the request.

The agenda for a general meeting of shareholders must include such items requested by one or more shareholders representing at least 3% of the issued share capital of a company or such lower percentage as the articles of association may provide. Our articles of association do not state such lower percentage.

Delaware. Delaware law does not specifically grant stockholders the right to bring business before an annual or special meeting. However, if a Delaware corporation is subject to the SEC's proxy rules, a stockholder who owns

at least $2,000 in market value, or 1% of the corporation's securities entitled to vote, may propose a matter for a vote at an annual or special meeting in accordance with those rules.

Action by written consent

The Netherlands. Under Dutch law, the articles of association of a company may provide that shareholders' resolutions may be adopted in writing without holding a general meeting of shareholders, provided that the resolution is adopted unanimously by all shareholders that are entitled to vote. For a listed company, this method of adopting resolutions is not feasible.

Delaware. Although permitted by Delaware law, publicly listed companies do not typically permit stockholders of a corporation to take action by written consent.

Appraisal rights

The Netherlands. The concept of appraisal rights does not exist under Dutch law. However, pursuant to Dutch law a shareholder who for its own account contributes at least 95% of our issued share capital may initiate proceedings against our minority shareholders jointly for the transfer of their shares to it. The proceedings are held before the Enterprise Chamber (*Ondernemingskamer*). 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 to be paid for the shares of the minority shareholders.

Furthermore, in accordance with Directive 2005/56/EC of the European Parliament and the Council of October 26, 2005 on cross-border mergers of limited liability companies, Dutch law provides that, to the extent the acquiring company in a cross-border merger is organized under the laws of another EU member state, a shareholder of a Dutch disappearing company who has voted against the cross-border merger may file a claim with the Dutch company for compensation. The compensation is to be determined by one or more independent experts.

Delaware. The Delaware General Corporation Law provides for stockholder appraisal rights, or the right to demand payment in cash of the judicially determined fair value of the stockholder's shares, in connection with certain mergers and consolidations.

Shareholder suits

The Netherlands. In the event a third party is liable to a Dutch company, only a company itself can bring a civil action against that third party. An individual shareholder does not have the right to bring an action on behalf of a company. This individual shareholder may, in its own name, have an individual right to take action against such third party in the event that the cause for the liability of that third party also constitutes a tortious act directly against that individual shareholder. The Dutch Civil Code provides for the possibility to initiate such action collectively. A collective action can be instituted by a foundation or an association whose objective is to protect the rights of a group of persons having similar interests. The collective action itself cannot result in an order for payment of monetary damages but may only result in a declaratory judgment (*verklaring voor recht*). In order to obtain compensation for damages, the foundation or association and the defendant may reach—often on the basis of such declaratory judgment—a settlement. A Dutch court may declare the settlement agreement binding upon all the injured parties with an opt-out choice for an individual injured party. An individual injured party may also itself—outside the collective action—institute a civil claim for damages.

Delaware. Under the Delaware General Corporation Law, a stockholder may bring a derivative action on behalf of the corporation to enforce the rights of the corporation. An individual also may commence a class action suit on behalf of himself and other similarly situated stockholders where the requirements for maintaining a class action under Delaware law have been met. A person may institute and maintain such a suit only if that person was a stockholder at the time of the transaction which is the subject of the suit. In addition, under Delaware case law, the plaintiff normally must be a stockholder at the time of the transaction that is the subject of the suit and throughout the duration of the derivative suit. Delaware law also requires that the derivative plaintiff make a demand on the directors of the corporation to assert the corporate claim before the suit may be prosecuted by the derivative plaintiff in court, unless such a demand would be futile.

Repurchase of shares

The Netherlands. Under Dutch law, a company such as ours may not subscribe for newly issued shares in its own share capital. Such company may, however, subject to certain restrictions under Dutch law and its articles of association, acquire shares in its own share capital. We may acquire fully paid-up shares in our own share capital at any time for no valuable consideration. Furthermore, subject to certain provisions of Dutch law and our articles of association, we may repurchase fully paid-up shares in our own share capital if (1) 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 applicable law and (2) we would not as a result of such repurchase hold more than 50% of our own issued share capital.

Other than shares acquired for no valuable consideration, ordinary shares may only be acquired following a resolution of our board, acting pursuant to an authorization for the repurchase of shares granted by the general meeting of shareholders. An authorization by the general meeting of shareholders for the repurchase 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. Our board has been authorized, for a period of 18 months to be calculated from the date of the annual general meeting of shareholders held on June 17, 2020, to cause the repurchase of ordinary shares by us of up to 10% of our issued share capital, for a price per share between the nominal value of the ordinary shares and an amount of 110% of the highest price of the ordinary shares officially quoted on any of the official stock markets we are listed on during any of 30 banking days preceding the date the repurchase is effected or proposed.

No authorization of the general meeting of shareholders is required if fully paid-up ordinary shares are acquired by us with the intention of transferring such ordinary shares to our employees under an applicable employee stock purchase plan, provided such ordinary shares are officially quoted on any of the official stock markets.

Delaware. Under the Delaware General Corporation Law, a corporation may purchase or redeem its own shares unless the capital of the corporation is impaired or the purchase or redemption would cause an impairment of the capital of the corporation. A Delaware corporation may, however, purchase or redeem out of capital any of its preferred shares or, if no preferred shares are outstanding, any of its own shares if such shares will be retired upon acquisition and the capital of the corporation will be reduced in accordance with specified limitations.

Anti-takeover provisions

The Netherlands. Under Dutch law, various protective measures are possible and permissible within the boundaries set by Dutch statutory law and Dutch case law. We have adopted several provisions that may have the effect of making a takeover of our company more difficult or less attractive, including:

- the staggered four-year terms of our directors, as a result of which only approximately one-fourth of our non-executive directors will be subject to election in any one year;
- a provision that our directors may only be removed at the general meeting of shareholders by a two-thirds majority of votes cast representing more than half of our issued share capital; and
- requirements 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 board.

Delaware. In addition to other aspects of Delaware law governing fiduciary duties of directors during a potential takeover, the Delaware General Corporation Law also contains a business combination statute that protects Delaware companies from hostile takeovers and from actions following the takeover by prohibiting some transactions once an acquirer has gained a significant holding in the corporation.

- Section 203 of the Delaware General Corporation Law prohibits "business combinations," including mergers, sales and leases of assets, issuances of securities and similar transactions by a corporation or a subsidiary with an interested stockholder that beneficially owns 15% or more of a corporation's voting stock, within three years after the person becomes an interested stockholder, unless: the transaction that will cause the person to become an interested stockholder is approved by the board of directors of the target prior to the transactions;
- after the completion of the transaction in which the person becomes an interested stockholder, the interested stockholder holds at least 85% of the voting stock of the corporation not including shares owned by persons who are directors and representatives of interested stockholders and shares owned by specified employee benefit plans; or
- after the person becomes an interested stockholder, the business combination is approved by the board of directors of the corporation and holders of at least 66.67% of the outstanding voting stock, excluding shares held by the interested stockholder.

A Delaware corporation may elect not to be governed by Section 203 by a provision contained in the original certificate of incorporation of the corporation or an amendment to the original certificate of incorporation or to the bylaws of the company, which amendment must be approved by a majority of the shares entitled to vote and may not be further amended by the board of directors of the corporation. Such an amendment is not effective until twelve months following its adoption.

Inspection of books and records

The Netherlands. Our board provides the shareholders, at the general meeting of shareholders, with all information that the shareholders require for the exercise of their powers, unless doing so would be contrary to an overriding interest of ours. Our board must give reason for electing not to provide such information on the basis of an overriding interest.

Delaware. Under the Delaware General Corporation Law, any stockholder may inspect certain of the corporation's books and records, for any proper purpose, during the corporation's usual hours of business.

Removal of directors

The Netherlands. Under our articles of association, the general meeting of shareholders is at all times entitled to suspend or dismiss a director. The general meeting of shareholders may only adopt a resolution to suspend or dismiss such a member by at least a two-thirds majority of the votes cast, provided such majority represents more than half of the issued share capital of our company.

Delaware. Under the Delaware General Corporation Law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (1) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board is classified, stockholders may effect such removal only for cause, or (2) in the case of a corporation having cumulative voting, if less than the entire board is to be removed, no director may be removed without cause if the votes cast against his removal would be sufficient to elect him if then cumulatively voted at an election of the entire board of directors, or, if there are classes of directors, at an election of the class of directors of which he is a part.

Preemptive rights

The Netherlands. Under Dutch law, in the event of an issuance of 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 (with the exception of ordinary shares to be issued to employees or ordinary shares issued against a contribution other than in cash). Under our articles of association, the preemptive rights in respect of newly issued ordinary shares may be restricted or excluded by a resolution of the general meeting of shareholders upon proposal of our board. The general meeting of shareholders may designate our board to restrict or exclude the preemptive rights in respect of newly issued ordinary shares. Such designation can be granted for a period not exceeding five years. A resolution of the general meeting of shareholders to restrict or exclude the preemptive rights or to designate the board as the authorized body to do so requires a two-thirds majority of the votes cast, if less than one half of our issued share capital is represented at the meeting.

At our annual general meeting of shareholders held on June 17, 2020, the general meeting of shareholders resolved to authorize our board for a period of 18 months with effect from the date of the meeting to restrict or exclude preemptive rights accruing to shareholders in connection with the issue of ordinary shares or rights to subscribe for ordinary shares.

Delaware. Under the Delaware General Corporation Law, stockholders have no preemptive rights to subscribe for additional issues of stock or to any security convertible into such stock unless, and to the extent that, such rights are expressly provided for in the certificate of incorporation.

Dividends

The Netherlands. Dutch law provides that dividends may be distributed after adoption of the annual accounts by the general meeting of shareholders from which it appears that such dividend distribution is allowed. Moreover, dividends may be distributed only to the extent that the shareholders' equity exceeds the amount of the paid-up and called-up part of the issued share capital of the company and the reserves that must be maintained under the law or the articles of association. Interim dividends may be declared as provided in the articles of association and may be distributed to the extent that the shareholders' equity exceeds the amount of the paid-up and called-up part of the issued share capital of the company and the reserves that must be maintained under the law or the articles of association, as apparent from an interim statement of assets and liabilities.

Under our articles of association, any amount of profit may be carried to a reserve as our board determines. After reservation by our board of any profit, the remaining profit will be at the disposal of the shareholders. Our corporate policy is to only make a distribution of dividends to our shareholders after the adoption of our annual accounts demonstrating that such distribution is legally permitted. However, our board is permitted to declare interim dividends without the approval of the general meeting of shareholders.

Dividends will be made payable not later than thirty days after the date they were declared unless the body declaring the dividend determines a different date. Claims to dividends not made within five years and one day from the date that such dividends became payable will lapse and any such amounts will be considered to have been forfeited to us (*verjaring*).

Delaware. Under the Delaware General Corporation Law, a Delaware corporation may pay dividends out of its surplus (the excess of net assets over capital), or in case there is no surplus, out of its net profits for the fiscal year in which the dividend is declared and/or the preceding fiscal year (provided that the amount of the capital of the corporation is not less than the aggregate amount of the capital represented by the issued and outstanding stock of all classes having a preference upon the distribution of assets). In determining the amount of surplus of a Delaware corporation, the assets of the corporation, including stock of subsidiaries owned by the corporation, must be valued at their fair market value as determined by the board of directors, without regard to their historical book value. Dividends may be paid in the form of shares, property or cash.

Shareholder vote on certain reorganizations

The Netherlands. Under Dutch law, the general meeting of shareholders must approve resolutions of the board relating to a significant change in the identity or the character of the company or the business of the company, which includes:

- a transfer of the business or virtually the entire business to a third party;
- the entry into or termination of a long-term cooperation of the company or a subsidiary with another legal entity or company or as a fully liable partner in a limited partnership or general partnership, if such cooperation or termination is of a far-reaching significance for the company; and
- the acquisition or divestment by the company or a subsidiary of a participating interest in the capital of a company having a value of at least one third of the amount of its assets according to its balance sheet and explanatory notes or, if the company prepares a consolidated balance sheet, according to its consolidated balance sheet and explanatory notes, according to the last adopted annual accounts of the company.

Delaware. Under the Delaware General Corporation Law, the vote of a majority of the outstanding shares of capital stock entitled to vote thereon generally is necessary to approve a merger or consolidation or the sale of all or substantially all of the assets of a corporation. The Delaware General Corporation Law permits a corporation to include in its certificate of incorporation a provision requiring for any corporate action the vote of a larger portion of the stock or of any class or series of stock than would otherwise be required.

Under the Delaware General Corporation Law, no vote of the stockholders of a surviving corporation to a merger is needed, however, unless required by the certificate of incorporation, if (1) the agreement of merger does not amend in any respect the certificate of incorporation of the surviving corporation, (2) the shares of stock of the surviving corporation are not changed in the merger and (3) the number of shares of common stock of the surviving corporation into which any other shares, securities or obligations to be issued in the merger may be converted does not exceed 20% of the surviving corporation's common stock outstanding immediately prior to the effective date of the merger. In addition, stockholders may not be entitled to vote in certain mergers with other corporations that own 90% or more of the outstanding shares of each class of stock of such corporation, but the stockholders will be entitled to appraisal rights.

Remuneration of directors

The Netherlands. Under Dutch law and our articles of association, we must adopt a remuneration policy for our directors. Such remuneration policy shall be adopted by the general meeting of shareholders upon the proposal of our non-executive directors. The remuneration of our executive directors will be determined by our non-executive directors with due observance of our remuneration policy; the remuneration of our non-executive directors will be determined by the board with due observance of our remuneration policy.

Delaware. Under the Delaware General Corporation Law, the stockholders do not generally have the right to approve the compensation policy for directors or the senior management of the corporation, although certain aspects of executive compensation may be subject to binding or advisory stockholder votes due to the provisions of U.S. federal securities and tax law, as well as stock exchange requirements.

Transfer Agent and Registrar

Computershare Trust Company, N.A. serves as transfer agent and registrar for our ordinary shares.

Exhibit 10.57

Confidential
Execution Version

Portions of this exhibit have been omitted for confidential treatment pursuant to Item 601(b)(10)(iv) of Regulation S-K.

AMENDMENT TO COLLABORATION AND LICENSE AGREEMENT

This **AMENDMENT TO THE COLLABORATION AND LICENSE AGREEMENT** (the "**Amendment**") is effective as of December 1, 2020 (the "**Amendment Effective Date**"), by and between **UNIQURE BIOPHARMA B.V.**, a corporation organized under the laws of the Netherlands, having its principal place of business at Paasheuvelweg 25a, 1105 BP Amsterdam, The Netherlands ("**uniQure**"), and **BRISTOL-MYERS SQUIBB COMPANY**, a Delaware corporation headquartered at 430 E. 29 Street, 14 Floor, New York, New York, USA 10016. **UNIQURE N.V.** is a party to this Agreement solely for purposes of Section 2. uniQure and BMS are sometimes referred to herein individually as a "**Party**" and collectively as the "**Parties**".

RECITALS

A. uniQure and BMS are parties to that certain Collaboration and License Agreement, dated April 6, 2015 (the "**Agreement**"), pursuant to which the Parties are collaborating to discover and develop gene therapy products for the treatment of cardiovascular diseases.

B. BMS and uniQure N.V., an Affiliate of uniQure, have also entered into that certain Investor Agreement (the "**Investor Agreement**"), that certain Share Subscription Agreement (the "**Subscription Agreement**"), that certain Seventh Collaboration Warrant Agreement, and that certain Tenth Collaboration Warrant Agreement (collectively, the "**Warrant Agreements**"), each one dated April 6, 2015.

C. The Parties now wish to concurrently amend the Agreement, in accordance with Section 17.1 thereof, to limit the number of Collaboration Targets and to modify the indication exclusivity provisions and certain financial terms, among other changes, and to terminate the Warrant Agreements.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual promises, covenants and conditions contained in this Amendment, uniQure and BMS, intending to be legally bound, agree as follows.

1. DEFINITIONS

Capitalized terms used in this Amendment that are not otherwise defined herein shall have the meanings such terms are given in the Agreement

2. TERMINATION OF WARRANT AGREEMENTS; CHANGE OF CONTROL PAYMENT

2.1 Warrant Agreements. BMS and uniQure N.V. hereby agree that on the Amendment Effective Date, each of the Warrant Agreements shall terminate and be of no further force and effect, without any exercise by BMS of its right to subscribe for and acquire from uniQure N.V. the Warrant Shares (as defined thereunder).

2.2 Payment upon Change of Control of uniQure. Subject to the provisions of this Section 2.2, substantially simultaneously with the consummation of the first Change of Control Transaction of uniQure that occurs prior to the earlier of (i) [*] anniversary of the Amendment Effective Date and (ii) BMS' delivery of a Target Cessation Notice for all four (4) Collaboration Targets, uniQure (or its Third Party acquirer) shall pay to BMS in Dollars via electronic funds transfer to an account designated by BMS a one-time, non-refundable, non-creditable cash payment (the "**Change of Control Payment**") of seventy million dollars ($70,000,000), provided that (x) if seventy million dollars ($70,000,000) is greater than five percent (5.0%) of the Net Proceeds from such Change of Control Transaction, the Change of Control Payment shall be an amount equal to five percent (5.0%) of such Net Proceeds, and (y) if seventy million dollars ($70,000,000) is less than one percent (1.0%) of such Net Proceeds, the Change of Control Payment shall be an amount equal to one percent (1.0%) of such Net Proceeds. For the avoidance of doubt, the sale or transfer of uniQure N.V. constitutes a Change of Control Transaction as set forth in subsection (3) of the definition of Change of Control Transaction (set forth in the Agreement). [*]. Net Proceeds shall be calculated as set forth in **Schedule 2.2**. For clarity, (a) the foregoing payment shall apply only to the first Change of Control Transaction of uniQure and not to any subsequent Change of Control Transaction and (b) the foregoing payment shall be in addition to any amounts paid or payable to BMS in connection with a Change of Control Transaction in respect of any equity securities of uniQure (or any of its Affiliates) held by BMS at such time or in respect of any other agreement, understanding or arrangement between uniQure and BMS, or their respective Affiliates, at such time.

2.3 Target Cessation Notice. With respect to each Collaboration Target, BMS shall, in good faith, notify uniQure in writing promptly following BMS' termination of all research, Development and Commercialization (if applicable) of all Target Therapeutics for such Collaboration Target (such notice, a "**Target Cessation Notice**").

3. AMENDMENT OF THE AGREEMENT

3.1 Research Program. The Parties agree that, notwithstanding anything in the Agreement to the contrary:

(a) the Research Term expired at the end of the Initial Research Term on May 21, 2019;

(b) notwithstanding such expiration of the Research Term, the Parties shall continue to conduct the Research Program under the Research Plan in accordance with the terms of the Agreement, until the earlier of [*];

(c) from and after the Amendment Effective Date, there shall be no more than four (4) Collaboration Targets;

(d) as of the Amendment Effective Date, the Collaboration Targets and the Exclusive Indications that BMS is pursuing are those set forth in **Schedule 3.1** (such Targets, the "**Existing Collaboration Targets**"), and all of the Existing Collaboration Targets are BMS Proprietary Targets;

(e) as of the Amendment Effective Date, there are no Reserved Targets and no Targets in which BMS is potentially interested that are subject to the terms of Section 3.4(d) of the Agreement;

(f) from and after the Amendment Effective Date, BMS shall have no rights to designate new Collaboration Targets under Section 3.3(a) or 3.3(c)(i) of the Agreement;

(g) during the Replacement Period, BMS shall have the right to designate [*] Reserved Targets for one or more Cardiovascular Disease(s) using the process in Section 3.4 of the Agreement, Section 3.3(b) of the Agreement will not apply to the designation of such Reserved Targets, such Reserved Targets shall be BMS Proprietary Targets, and during the Replacement Period, uniQure shall have no right to, directly or indirectly, have any discussions or engage in any other activities with any Third Party regarding a possible collaboration or license with respect to any Reserved Target or any Variant thereof nor any right to initiate or engage in any other activities with respect to an internal program for any Reserved Target or any Variant thereof; and

(h) from and after the Amendment Effective Date, BMS shall have the right to replace [*] Collaboration Targets with Replacement Targets pursuant to Section 3.3(c)(ii) of the Agreement, as amended below.

For clarity, (A) in the event that BMS designates any Target as a Reserved Target during the Replacement Period, at the end of the Replacement Period, any Reserved Target will cease to be a Reserved Target, and (B) BMS will have no right to designate any Target as a Reserved Target after the Replacement Period.

3.2 Amendment of Article 1; Certain Defined Terms.

(a) The definition of "**Therapeutic**" in Section 1.175 of the Agreement is hereby deleted and replaced with the following:

> "**Therapeutic**" means (a) any Target Therapeutic discovered, owned or Controlled by or for uniQure or any of its Affiliates as part of the performance of the Research Program, (b) any Target Therapeutic for a Collaboration Target discovered by or for uniQure or any of its Affiliates (i.e., whether or not as part of the performance of the Research Program) as of the Effective Date or thereafter during the Term, (c) any peptide or any AAV derived vector with a Collaboration Target that is generically or specifically claimed by a Valid Claim of the uniQure Patents, (d) any Target Therapeutic discovered by BMS or any other Related Party as part of the performance of the Research Program, and (e) any Target Therapeutic for a Collaboration Target which BMS' manufacture, approved use or sale thereof would infringe a Valid Claim of the uniQure Patents but for the exclusive license granted to BMS under this Agreement. For clarity, the inclusion of "Collaboration Target" in clause (c) does not limit the AAV derived vectors that are included in the uniQure Technology licensed to BMS under this Agreement.

New Defined Terms. Article 1 of the Agreement is hereby amended to add the following new definitions:

"**CoC Opt-Out Period**" has the meaning set forth in the definition of Indication Exclusivity Opt-Out Period.

"**Exclusive Indication**" means [*].

"**Non-Exclusive Indication**" means [*].

"**Indication Exclusivity Opt-Out Period**" means (a) the period commencing on the Amendment Effective Date and ending on [*] anniversary of the Amendment Effective Date, and (b) if the first Change of Control Transaction of uniQure occurs after [*] anniversary of the Amendment Effective Date, the [*] period following the effective date of such Change of Control Transaction (such [*] period, the "**CoC Opt-Out Period**").

"**Replacement Period**" has the meaning set forth in Section 3.3(c)(ii).

3.3 Replacement Targets. Section 3.3(c)(ii) of the Agreement is hereby deleted and replaced with the following:

(ii) Replacing a Collaboration Target. During the period from the Amendment Effective Date until [*] anniversary thereof (the "**Replacement Period**"), BMS shall have the right to replace any of the Existing Collaboration Targets, and after the first such replacement, any then-current Collaboration Target, with a new Target for one or more Cardiovascular Disease(s) (a "**Replacement Target**") in accordance with and subject to the Excluded Target process as described in Section 3.4; *provided however*, that (A) BMS may replace a Collaboration Target hereunder no more than [*], and (B) if BMS is replacing a Collaboration Target with a Reserved Target, BMS may do so by written notice to the JSC without following the Excluded Target process in Section 3.4. For the avoidance of doubt, no Target Designation Fee is due or payable for a Replacement Target.

3.4 Excluded Targets and Non-Exclusive Indications. Section 3.4 of the Agreement is hereby deleted and replaced with the following:

Excluded Target and Non-Exclusive Indication Process; Designation of Reserved Targets and Replacement Targets for Collaboration Targets.

(a) **Target Reviewer.**

(i) If, during the Replacement Period, BMS desires to add a Reserved Target (which BMS may do [*]) or propose a new Target as a Replacement Target for a Collaboration Target, BMS shall notify uniQure through the Joint Discovery Working Group of (A) such Target, (B) the Collaboration Target that is being replaced (if applicable), and (C) the proposed Exclusive Indication(s) for which BMS intends to Develop Therapeutics, which Exclusive Indications may be Cardiovascular Diseases only. Within [*] after such notification, uniQure shall provide an independent reviewer mutually agreed to by BMS and uniQure (the "**Target Reviewer**") with an updated Excluded Target list (which shall include the Target identification information for each Excluded Target) and Non-Exclusive Indication list. Within [*] after uniQure has provided the Target Reviewer with such updated Excluded Target list and Non-Exclusive Indication list, BMS shall provide to the Target Reviewer the Target BMS proposes to become a Replacement Target (and thereby, a Collaboration Target) or Reserved Target and the corresponding proposed Exclusive Indication(s). Within [*] thereafter, the Target Reviewer shall notify BMS whether or not the proposed Target is an Excluded Target and, if such proposed Target is not an Excluded Target, whether or not each of the proposed Exclusive Indications is a Non-Exclusive Indication. If the proposed Target is not an Excluded Target, BMS shall then

have the right to designate such Target as a Collaboration Target or Reserved Target, as the case may be, in accordance with Section 3.4(b). [*].

(ii) In the case where BMS is considering a Target as a potential Replacement Target or potential Reserved Target and does not want to bring such Target to the attention of uniQure through the Joint Discovery Working Group before determining whether such Target is an Excluded Target, then BMS shall request uniQure to provide an updated Excluded Target list and updated Non-Exclusive Indication list to the Target Reviewer within [*] after such request without obligation to specify the Target or proposed Exclusive Indication for which the Target Reviewer process shall be initiated. Within [*] after uniQure has provided the Target Reviewer with such updated lists, BMS shall provide to the Target Reviewer the Target BMS proposes to become a Replacement Target or Reserved Target and the proposed Exclusive Indication(s). Within [*] thereafter, the Target Reviewer shall notify BMS whether or not the proposed Target is an Excluded Target and, if such proposed Target is not an Excluded Target, whether or not each of the proposed indications is a Non-Exclusive Indication. If the proposed Target is not an Excluded Target, BMS shall have the right to designate such Target as a Collaboration Target or Reserved Target, as the case may be, in accordance with Section 3.4(b). BMS [*] and shall not be obliged to disclose to uniQure for which Target the Target Reviewer function was performed.

(b) **Consultation with uniQure; Designation of Reserved Target or Replacement Target for a Collaboration Target and any Exclusive Indication(s).** Promptly after the Target Reviewer has indicated that the proposed Target is not an Excluded Target, BMS shall notify uniQure through the Joint Discovery Working Group with respect to such proposed Target, including providing the Joint Discovery Working Group the Target identification information with respect to such Target and proposed Exclusive Indications for such Target. The Joint Discovery Working Group shall discuss the proposed Collaboration Target or Reserved Target, as the case may be, and the proposed Exclusive Indications for such Target; *provided however*, that BMS shall have the final decision making authority with respect to the designation of a proposed Target as a Collaboration Target or Reserved Target, as the case may be, provided that such Target is not an Excluded Target. BMS may designate such Target as a Collaboration Target or Reserved Target, as the case may be, by written notification to uniQure, and in conjunction with the designation of such proposed Target as a Collaboration Target by BMS, uniQure shall deliver a certificate for such proposed Target substantially in the form attached to this Agreement as **Exhibit G**. Where a proposed indication is a Non-Exclusive Indication at the time such Target is designated as a Collaboration Target, or if there is no scientific rationale or therapeutic applicability for such proposed Exclusive Indication, then such indication will not be an Exclusive Indication. Where a proposed indication is a Non-Exclusive Indication at the time such Target is designated as a Reserved Target, or if there is no scientific rationale or therapeutic applicability for such indication, when and if such Reserved Target is subsequently designated by BMS as a Replacement Target, such indication will not be an Exclusive Indication.

(c) **Adding a New Exclusive Indication**. If, during the Replacement Period, BMS desires to propose a new potential Exclusive Indication for

any Collaboration Target, BMS shall notify uniQure of such potential Exclusive Indication for which BMS intends to Develop Therapeutics through the Joint Discovery Working Group. Within [*] after such notification, uniQure shall provide a Target Reviewer with an updated Non-Exclusive Indication list. Within [*] after uniQure has provided the Target Reviewer with such updated Non-Exclusive Indication list, BMS shall provide to the Target Reviewer the proposed Non-Exclusive Indication. Within [*] thereafter, the Target Reviewer shall notify BMS whether or not the proposed Exclusive Indication is a Non-Exclusive Indication. If the proposed Exclusive Indication is not a Non-Exclusive Indication and there is a scientific rationale and therapeutic applicability for such indication, it will become an Exclusive Indication, and BMS will promptly thereafter provide an updated Development Plan including Development activities for such Exclusive Indication to the JSC. BMS shall pay all fees and expenses of the Target Reviewer for performing this Target Reviewer function. For clarity, BMS shall not have the right to add an Exclusive Indication after the Replacement Period.

(d) **Alternative Procedure.** For purposes of the designation of any particular Target as a Replacement Target or Reserved Target or the designation of any indication as an Exclusive Indication, the Parties may mutually agree to not utilize the Target Reviewer, and instead allow the Joint Discovery Working Group to consider any particular Target as a Replacement Target or Reserved Target and any indication as an Exclusive Indication, and allow BMS to designate such particular Target as a Replacement Target or Reserved Target or such indication as an Exclusive Indication without utilizing the Target Reviewer.

3.5 Manufacturing. Section 6.2 of the Agreement is hereby deleted and replaced with the following:

Manufacturing Overview.

(a) Within the scope of the licenses granted in Section 7.1(a) and (b) and subject to the payment obligations of BMS pursuant to Article 8 and the provisions set forth in Section 6.3, BMS shall, notwithstanding anything to the contrary herein, have (i) the exclusive right and will be solely responsible for the manufacture of Therapeutics that are not for Gene Therapy (e.g., peptides) and Products containing such Therapeutics ("**Non-Gene Therapy Therapeutics**" and "**Non-Gene Therapy Products**", respectively) itself or through one or more Affiliates or Third Parties selected by BMS, and (ii) the right, but not the obligation, to manufacture Therapeutics that are for Gene Therapy and any Products containing any such Therapeutics itself or through one or more Affiliates or Third Parties selected by BMS. Where BMS exercises its right to so manufacture any amount of any Therapeutic that is for Gene Therapy and any Product containing any such Therapeutic, uniQure shall have no obligations in connection with the manufacture of such amount of such Therapeutic and such Product manufactured by BMS or its Affiliate or any Third Party.

(b) For all Therapeutics and Products that are for Gene Therapy, uniQure shall be responsible for the manufacture and supply of such Therapeutics and Products. Supply of Therapeutics for research and pre-clinical purposes will be conducted under **Schedule 3.5** to the Amendment. Clinical supply will be conducted pursuant to that certain Master Clinical Supply Agreement, dated April 25, 2017, as amended on the Amendment Effective Date, between uniQure and E.R. Squibb and Sons, LLC, an Affiliate of BMS (the "**Clinical Supply Agreement**"). The Parties (or their respective Affiliates) shall enter into a commercial supply agreement that shall contain the provisions set forth in **Exhibit J** except for those pertaining to clinical supply and the termination provisions, which shall be modified to permit BMS (or the Applicable Affiliate(s)) to terminate such commercial supply agreement in its entirety or on a Collaboration Target-by-Collaboration Target, Therapeutic-by-Therapeutic or Product-by-Product basis and to terminate any statement of work under such commercial supply agreement at any time without

cause on [*] prior written notice, in each case subject to payments, if any, to uniQure set forth in such agreement (the "**Commercial Supply Agreement**"), and shall enter into the Commercial Supply Agreement no later than [*]. **Schedule 3.5** of the Amendment, the Clinical Supply Agreement and the Commercial Supply Agreement are hereinafter, individually and collectively, the "**Supply Agreement(s)**". Notwithstanding anything to the contrary in this Agreement or any Supply Agreement, BMS (or the applicable Affiliate(s)) may terminate any Supply Agreement in its entirety or on a Collaboration Target-by-Collaboration Target, Therapeutic-by-Therapeutic or Product-by-Product basis and may terminate any statement of work under any Supply Agreement at any time without cause on [*] prior written notice, in each case subject to payments, if any, to uniQure set forth in the applicable Supply Agreement. For clarity, nothing contained herein will limit any of BMS' rights hereunder, including BMS' right to manufacture Therapeutics that are for Gene Therapy and any Products containing any such Therapeutics itself or through one or more Affiliates or Third Parties selected by BMS as set out in Section 6.2(a).

(c) Notwithstanding anything to the contrary herein or in any of the Supply Agreement(s), (i) uniQure shall conduct its manufacture and supply obligations hereunder and under the Supply Agreement(s) using [*], and (ii) if BMS desires that any Therapeutic be manufactured and supplied using [*], the "**Other Platforms**"), BMS shall have the right to manufacture and supply, or have manufactured and supplied, any or all of its requirements of any such Therapeutic using any Other Platform and shall be solely responsible for such manufacture and supply, at its sole expense, and uniQure shall have no rights or obligations in connection with such manufacture and supply (and, for clarity, (A) neither BMS nor any of its Affiliates will have any obligations to uniQure hereunder or otherwise with respect to such manufacture and supply of any Therapeutic using any such Other Platform, and (B) for as long as a Collaboration Target remains a Collaboration Target, any Therapeutics and Products manufactured for such Collaboration Target using any Other Platform will be subject to all other terms of the Agreement, including all payment obligations of BMS, except that there will be no payment obligation for the Manufacturing Cost-Based Component of Supply Price).

3.6 Third Party Manufacturing. Section 6.3 of the Agreement is hereby deleted and replaced with the following:

Third Party Manufacturing. Within the scope of the licenses granted in Section 7.1(a) and (b) and subject to the payment obligations of BMS pursuant to Article 8 and the provisions set forth in Section 6.2, BMS may exercise any of its manufacturing rights (including any have made rights) with respect to any (i) Non-Gene Therapy Therapeutics and Non-Gene Therapy Products, and (ii) Therapeutics and Products for Gene Therapy, in each case, through one or more Third Party manufacturers; *provided however*, that the Third Party manufacturer undertakes in writing obligations of confidentiality and non-use regarding Confidential Information of uniQure (including uniQure Manufacturing Technology received by such Third Party manufacturer) that are consistent with those undertaken by the Parties pursuant to Article 12 hereof; *provided further*, that [*]. Such Third Party manufacturers shall be obligated in writing not to use the uniQure Know-How and uniQure Manufacturing Technology for any use, other than [*].

3.7 Restatement of Exclusive License and Limitations. Sections 7.1(a) and 7.1(e) of the Agreement are hereby restated as the following Section 7.1(a):

(a) Exclusive License Grant. Subject to the terms and conditions of this Agreement and the terms and conditions of any Third Party agreement that are applicable to a sublicensee under such Third Party agreement (including the Existing License Agreements), uniQure hereby grants to BMS an exclusive (even as to uniQure, except as provided in Section 7.3) license, with the right to grant sublicenses (through

multiple tiers) as provided in Section 7.2, under the uniQure Technology to research, develop, make, have made, use, sell, offer for sale, export and import (including the exclusive right to Develop and Commercialize) Collaboration Targets, Therapeutics and Products in the Field in the Territory. Without limiting the generality of the foregoing terms of this Section 7.1(a), the license granted by uniQure to BMS pursuant to this Section 7.1(a) shall include, subject to the terms and conditions of this Agreement and the terms and conditions of any Third Party agreement that are applicable to a sublicensee under such Third Party agreement (including the Existing License Agreements), an exclusive (even as to uniQure, except as provided in Section 7.3) sublicense, with the right to grant sublicenses (through multiple tiers) as provided in Section 7.2, under the Information and Patents included in the uniQure Technology and licensed to uniQure under any Third Party Agreements to which uniQure is a party, to research, develop, make, have made, use, sell, offer for sale, export and import (including the exclusive right to Develop and Commercialize) Collaboration Targets, Therapeutics and Products in the Field in the Territory. For clarity, BMS' licenses under this Section 7.1(a) and Sections 7.1(b) and (c) shall cover only Collaboration Targets, and Therapeutics and Products with respect to the applicable Collaboration Target, and only for so long as the applicable Collaboration Target remains a Collaboration Target (i.e., has not been replaced or terminated). Accordingly, the licenses under this Section 7.1 with respect to a particular Collaboration Target, and Therapeutics and Products with respect to such Collaboration Target, shall terminate when such Collaboration Target is terminated or replaced and is therefore no longer a Collaboration Target. For further clarity, subject to the terms of this Agreement and any Supply Agreement, BMS and its Affiliates shall have the right to use Third Parties to assist with, and/or to conduct, discovery, research, development, pre-clinical, clinical, commercial and other activities with respect to the Therapeutics for the Collaboration Targets, including studies, testing and validation, and the right for BMS to make and have made Therapeutics and research grade and other materials (including uniQure Materials) (itself or by any of its Affiliates or any Third Parties selected by BMS) to conduct research, pre-clinical, development, commercial and other activities.

3.8 Indication Exclusivity. Section 11.1(d) of the Agreement (which for clarity includes only the first clause thereof and not the subsequent paragraphs) is hereby deleted and replaced with the following:

"for as long as BMS is pursuing the Development of or is Commercializing a Therapeutic or Product for any Exclusive Indication, with respect to discovery, research, Development or Commercialization activities for such Exclusive Indication in the Field in the Territory (including with respect to discovery or research activities for the purpose of identifying Target Therapeutics for such Exclusive Indication)."

3.9 Indication Exclusivity Opt-Out. A new Section 11.2 is hereby added to the Agreement as follows:

Indication Exclusivity Opt-Out. At any time during the Indication Exclusivity Opt-Out Period, uniQure (or as the case may be, its successor in interest) may opt out of the exclusivity obligations under Section 11.1(d) with respect to a particular indication by written notice to BMS (such notice, the "**Opt-Out Notice**" and such indication, the "**Opt-Out Indication**"). uniQure may exercise such right to opt out up to [*]. Upon BMS' receipt of the Opt-Out Notice (the "**Opt-Out Exercise**"), the following will apply:

(a) All payments under Sections 8.3, 8.4 and 8.5 will be reduced by [*] of the amounts otherwise payable under such sections and, in addition, if the Opt-Out Exercise occurs during the CoC Opt-Out Period, uniQure shall refund to BMS [*] of all amounts previously paid by BMS under Sections 8.3, 8.4 and 8.5. Such reduction will apply for each Opt-Out Exercise. For example, [*]. For the avoidance of doubt, and notwithstanding anything contained herein to the contrary, for each Opt-Out Exercise, payments under Sections 8.3, 8.4 and 8.5 will be reduced for all of the Collaboration Targets, not just the Collaboration Target(s) for which the Opt-Out Indication is being worked on by BMS.

(b) BMS shall not be obligated to inform the JSC or any subcommittees or working groups of its Development activities with respect to Therapeutics and Products for the Collaboration Target to which the Opt-Out Indication relates, to the extent such activities are for the Opt-Out Indication, except to the extent necessary for uniQure to conduct its obligations under this Agreement or any separate agreement for the supply of Therapeutics and Products for Gene Therapy for research purposes or any Supply Agreement.

(c) uniQure shall establish and maintain appropriate firewalls to segregate its independent activities on the Opt-Out Indication and its personnel (and, if applicable, those of its Third Party collaborator) conducting such activities from activities performed by or on behalf of BMS or its Affiliates under this Agreement or any Supply Agreement, in each case for the Collaboration Target(s) to which such Opt-Out Indication relates and the personnel performing such activities, (A) to ensure that no BMS Confidential Information and no Information generated under this Agreement or any Supply Agreement is disclosed to any of such personnel performing such independent activities or used in connection with such independent activities, other than [*], and (B) to ensure that any and all intellectual property (including know-how, patents, copyright, trademarks and trade secrets), regulatory materials, regulatory filings and approvals, materials and other proprietary Information generated in connection with such independent activities on the Opt-Out Indication [*] will be segregated from activities performed pursuant to this Agreement or any Supply Agreement. Without limiting the foregoing, such firewalls will include all personnel conducting manufacturing activities, including manufacturing development (e.g., analytical development and process development) [*].

For clarity, the Opt-Out Exercise applies only to exclusivity with respect to the Opt-Out Indication under Section 11.1(d), and will not affect exclusivity under Section 11.1(c) with respect to any Collaboration Target. For further clarity, when uniQure exercises an Opt-Out Exercise, uniQure shall have no right to work on any Collaboration Target or Variant thereof, including on any Therapeutic for any Collaboration Target for any indication, except as permitted under the paragraphs of Section 11.1 that follow Section 11.1(d).

4. MISCELLANEOUS

4.1 Full Force and Effect. This Amendment amends the terms of the Agreement and is deemed incorporated into the Agreement. The provisions of the Agreement, as amended by this Amendment, remain in full force and effect.

4.2 Counterparts. This Amendment may be executed in one or more counterparts, each of which will be an original and all of which together will constitute one instrument and may be executed and delivered through the use of facsimiles or email of pdf copies of this executed Amendment, and each such scanned or pdf copy of this Amendment that includes a Party's signature will be deemed an original.

IN WITNESS WHEREOF, BMS, uniQure and uniQure N.V. have executed this Amendment, effective as of the Amendment Effective Date.

BRISTOL-MYERS SQUIBB COMPANY

By: /s/ [*]

Name:[*]

Title: [*]

UNIQURE BIOPHARMA B.V.

By: /s/ Christian Klemt

Name: Christian Klemt

Title: Chief Accounting Officer & Director

Solely for purposes of Section 2:

UNIQURE N.V.

By: /s/ Matthew Kapusta

Name:Matthew Kapusta

Title: Chief Executive Officer & Executive Director

Schedule 2.2
Net Proceeds; Calculation of Change of Control Payment

[*]

Schedule 3.1
Existing Collaboration Targets and Exclusive Indications

The four Existing Collaboration Targets and Exclusive Indications are:

[*]

Schedule 3.5
Research Supply Terms

This Schedule 3.5 includes terms and conditions for the supply of research materials by uniQure to BMS.

[*]

Exhibit 10.58

EXECUTION VERSION

Portions of this exhibit have been omitted for confidential treatment pursuant to Item 601(b)(10)(iv) of Regulation S-K.

AMENDMENT NO. 2 TO SECOND AMENDED AND RESTATED LOAN AND SECURITY AGREEMENT

This **AMENDMENT NO. 2 TO SECOND AMENDED AND RESTATED LOAN AND SECURITY AGREEMENT** (this "**Amendment**"), is dated as of January 29, 2021 and is entered into by and among (a) (i) **UNIQURE BIOPHARMA B.V.**, a private limited liability company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 34275365 ("**uniQure Bio**"), (ii) **UNIQURE, INC.**, a Delaware corporation ("**US Borrower**" and together with uniQure Bio hereinafter collectively referred to as "**Borrower**"), (iii) **UNIQURE IP B.V.**, a private limited liability company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 34275369 ("**uniQure IP**"), and (iv) **UNIQURE N.V.** (formerly uniQure B.V.), a public limited company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 54385229 ("**uniQure Holdings**" and together with Borrower and uniQure IP, the "**Obligors**"), (b) **HERCULES CAPITAL, INC.**, a Maryland corporation in its capacity as administrative agent for itself and the Lender (as defined herein) (in such capacity, the "**Agent**"), and (c) the several banks and other financial institutions or entities from time to time parties to the Loan Agreement (collectively, referred to as "**Lender**"). Capitalized terms used herein without definition shall have the same meanings given them in the Amended Loan Agreement (as defined below).

RECITALS

A. **WHEREAS**, Obligors, Agent and Lender have entered into that certain Second Amended and Restated Loan and Security Agreement, dated as of May 6, 2016, as amended by Amendment No. 1 to Second Amended and Restated Loan and Security Agreement dated as of December 6, 2018 (as so amended and as may further be amended, restated, amended and restated, supplemented or otherwise modified from time to time, the "**Loan Agreement**"), pursuant to which Lender has agreed to extend and make available to Borrower certain advances of money;

B. **WHEREAS**, under the Loan Agreement, there are 2018 Term Loan Advances outstanding in the aggregate principal amount of Thirty-Five Million Dollars ($35,000,000) and Lender has not made any 2018 Term B Loan Advance to Borrower;

C. **WHEREAS**, Borrower has requested Lender to make available to Borrower term loans in an aggregate principal amount of up to One Hundred Million Dollars ($100,000,000); and

D. **WHEREAS**, Obligors and Lender have agreed to amend the Loan Agreement upon the terms and conditions more fully set forth herein.

AGREEMENT

NOW THEREFORE, in consideration of the foregoing Recitals and intending to be legally bound, the parties hereto agree as follows:

1. AMENDMENTS.

1.1. Subject to and upon the satisfaction of the conditions specified in Section 4 hereof, the Loan Agreement and certain schedules thereto are hereby amended to reflect the changes which are attached as Exhibit A hereto [*].

1.2. Each reference in the Loan Agreement to "this Agreement" and the words "hereof," "herein," "hereunder," or words of like import, shall mean and be a reference to the Loan Agreement as amended by this Amendment (the "**Amended Loan Agreement**").

2. BORROWER'S REPRESENTATIONS AND WARRANTIES. Borrower represents and warrants that:

2.1. Immediately upon giving effect to this Amendment (i) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date (in all cases without duplication of any standard(s) of materiality contained in the Loan Documents as to such representations and warranties) and (ii) no Event of Default has occurred and is continuing with respect to which Borrower has not been notified in writing by Agent or Lender.

2.2. Borrower has the corporate or other applicable company power and authority to execute and deliver this Amendment and to perform its obligations under the Amended Loan Agreement.

2.3. [Reserved.]

2.4. The execution and delivery by Borrower of this Amendment and the performance by Borrower of its obligations under the Amended Loan Agreement have been duly authorized by all necessary corporate or other applicable company action on the part of Borrower.

2.5. Subject to any matters which are set out as qualifications or reservations as to matters of law of general application in the legal opinions delivered to the Lender pursuant to Section 4, this Amendment has been duly executed and delivered by Borrower and is the binding obligation of Borrower, enforceable against it in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, liquidation, moratorium or other similar laws of general application and equitable principles relating to or affecting creditors' rights; and

2.6. As of the date hereof, it has no defenses against the obligations to pay any amounts under the Secured Obligations. Borrower acknowledges that each of Agent and Lender has acted in good faith and has conducted in a commercially reasonable manner its relationships with Borrower in connection with this Amendment and in connection with the Loan Documents.

Borrower understands and acknowledges that each of Agent and Lender is entering into this Amendment in reliance upon, and in partial consideration for, the above representations and warranties, and agrees that such reliance is reasonable and appropriate.

3. LIMITATION. The amendments set forth in this Amendment shall be limited precisely as written and shall not be deemed (a) to be a waiver or modification of any other term or condition of the

Loan Agreement or of any other instrument or agreement referred to therein or to prejudice any right or remedy which Agent and/or Lender may now have or may have in the future under or in connection with the Amended Loan Agreement or any instrument or agreement referred to therein; or (b) to be a consent to any future amendment or modification or waiver to any instrument or agreement the execution and delivery of which is consented to hereby, or to any waiver of any of the provisions thereof. Except as expressly amended hereby, the Loan Agreement shall continue in full force and effect.

4. **Effectiveness**. This Amendment shall become effective upon the satisfaction of all the following conditions precedent (the date of satisfaction of all such conditions precedent, the "**Second Amendment Effective Date**"):

4.1. **Amendment**. Obligors, Agent and Lender shall have duly executed and delivered this Amendment to Lender.

4.2. **Certificates of Authority and Incumbency**. Each Obligor shall have delivered to Agent a certificate, dated the Second Amendment Effective Date and executed by the secretary or equivalent officer of such Obligor, with appropriate insertions and attachments, including:

4.2.1. a copy of its respective certificate or deed of incorporation and current articles of association and bylaws, and for uniQure Bio an extract of its registration in the Trade Register of the Dutch Chamber of Commerce;

4.2.2. a copy of resolutions of its Board and general meeting of shareholders (to the extent required) evidencing approval of (a) this Amendment and the transactions contemplated thereby including the 2021 Term Loan Advances and (b) other transactions evidenced by the Loan Documents;

4.2.3. the names, titles, incumbency and signature specimens of those respective representatives of such Obligor who have been authorized by such resolutions and/or written consents to execute Loan Documents on behalf of such Person; and

4.2.4. for uniQure US, a certificate of good standing from its state of incorporation and similar certificates from all other jurisdictions in which such Borrower does business and where the failure to be qualified would have a Material Adverse Effect.

4.3. **Searches**. Agent shall have received the results of searches in Delaware, the District of Columbia and Massachusetts with respect to the applicable Obligors, and such searches shall reveal no liens on any of the assets of such Person except for Permitted Liens or Liens to be discharged on or prior to the Second Amendment Effective Date (which liens shall be discharged pursuant to documentation reasonably satisfactory to Agent).

4.4. **Perfection Certification**. Each Obligor shall have delivered to Agent an updated perfection certificate.

4.5. **Opinion Letters**. Agent shall have received a legal opinion of Lender's Dutch counsel.

4.6. Advance Request. An Advance Request in respect of the 2021 Term Loan Advance to be requested under Section 2.1.2(a)(i) of the Amended Loan Agreement as described in Section 4.2 of the Amended Loan Agreement.

4.7. Facility Charge. Borrower shall have paid to Agent a facility fee of three hundred fifty thousand dollars ($350,000).

4.8. Payment of Lender Expenses. Borrower shall have paid all reasonable and invoiced Lender expenses (including all reasonable and invoiced attorneys' fees and reasonable expenses) incurred through the date of this Amendment.

5. Release. In consideration of the agreements of Agent and each Lender contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Borrower, on behalf of itself and its successors, assigns, and other legal representatives, hereby to the extent possible under applicable law fully, absolutely, unconditionally and irrevocably releases, remises and forever discharges Agent and each Lender, and its successors and assigns, and its present and former shareholders, affiliates, subsidiaries, divisions, predecessors, directors, officers, attorneys, employees, agents and other representatives (Agent, Lenders and all such other persons being hereinafter referred to collectively as the "**Releasees**" and individually as a "**Releasee**"), of and from all demands, actions, causes of action, suits, covenants, contracts, controversies, agreements, promises, sums of money, accounts, bills, reckonings, damages and any and all other claims, counterclaims, defenses, rights of set-off, demands and liabilities whatsoever of every name and nature, known or unknown, suspected or unsuspected, both at law and in equity, which Borrower, or any of its successors, assigns, or other legal representatives may now or hereafter own, hold, have or claim to have against the Releasees or any of them for, upon, or by reason of any circumstance, action, cause or thing whatsoever which arises at any time on or prior to the day and date of this Amendment, for or on account of, or in relation to, or in any way in connection with the Loan Agreement, or any of the other Loan Documents or transactions thereunder or related thereto. Borrower understands, acknowledges and agrees that the release set forth above may be pleaded as a full and complete defense and may be used as a basis for an injunction against any action, suit or other proceeding which may be instituted, prosecuted or attempted in breach of the provisions of such release. Borrower agrees that no fact, event, circumstance, evidence or transaction which could now be asserted or which may hereafter be discovered shall affect in any manner the final, absolute and unconditional nature of the release set forth above.

6. Counterparts. This Amendment may be signed in any number of counterparts, and by different parties hereto in separate counterparts, with the same effect as if the signatures to each such counterpart were upon a single instrument. All counterparts shall be deemed an original of this Amendment. This Amendment may be executed by facsimile, portable document format (.pdf) or similar technology signature, and such signature shall constitute an original for all purposes.

7. Incorporation By Reference. The provisions of Section 10 (Miscellaneous) of the Loan Agreement shall be deemed incorporated herein by reference, *mutatis mutandis*.

8. Loan Documents. This Amendment shall constitute a Loan Document.

[*Remainder of this page intentionally left blank*]

IN WITNESS WHEREOF, the parties have duly authorized and caused this Amendment to be executed as of the date first written above.

BORROWER:

UNIQURE BIOPHARMA B.V.

Signature: /s/ Christian Klemt

Print Name: Christian Klemt

Title: Chief Accounting Officer Director

UNIQURE, INC.

Signature: /s/ Matt Kapusta

Print Name: Matt Kapusta

Title: Chief Executive Officer

OBLIGOR:

UNIQURE N.V. (formerly uniQure B.V.)

Signature: /s/ Matt Kapusta

Print Name: Matt Kapusta

Title: Chief Executive Officer

UNIQURE IP B.V.

Signature: /s/ Christian Klemt

Print Name: Christian Klemt

Title: Chief Accounting Officer Director

Accepted in Palo Alto, California:

AGENT:

HERCULES CAPITAL, INC.

By: /s/ [*]
Name: [*]
Its: [*]

LENDER:

HERCULES CAPITAL FUNDING TRUST 2018-1

By: /s/ [*]
Name: [*]
Its: [*]

HERCULES CAPITAL FUNDING TRUST 2019-1

By: /s/ [*]
Name: [*]
Its: [*]

HERCULES CAPITAL, INC.

By: /s/ [*]
Name: [*]
Its: [*]

EXHIBIT A

UNIQURE

SECOND AMENDED AND RESTATED LOAN AND SECURITY AGREEMENT

THIS SECOND AMENDED AND RESTATED LOAN AND SECURITY AGREEMENT is made and dated as of May 6, 2016 and is entered into by and among (i) UNIQURE BIOPHARMA B.V., a private limited liability company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 34275365 ("**uniQure Bio**"), (ii) UNIQURE, Inc., a Delaware corporation ("**US Borrower**" and together with uniQure Bio hereinafter collectively referred to as "**Borrower**"), (iii) UNIQURE IP B.V., a private limited liability company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 34275369 ("**uniQure IP**"), (iv) each of the subsidiaries of uniQure identified on the Schedule 1 hereto and the signature pages hereof ("**uniQure Subsidiaries**"), (v) UNIQURE N.V. (formerly uniQure B.V.), a public limited company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 54385229 ("**uniQure Holdings**" and together with uniQure IP, the uniQure Subsidiaries, and Borrower, the "**Obligors**"), (vi) the several banks and other financial institutions or entities from time to time parties to this Agreement (collectively referred to as "**Lender**"), and (vii) HERCULES CAPITAL, INC., a Maryland corporation, in its capacity as administrative agent and collateral agent for itself and the Lender (and in such capacity, the "**Agent**"), and as amended by (a) Amendment No. 1 to Second Amended and Restated Loan and Security Agreement, dated as of the First Amendment Closing Date (as defined below) (the "**Amendment No. 1**"), by and among the Obligors, Agent and Lender and (b) Amendment No. 2 to Second Amended and Restated Loan and Security Agreement, dated as of the Second Amendment Closing Date (as defined below) (the "**Amendment No. 2**"), by and among the Obligors, Agent and Lender (as so amended and as may be further amended, restated, amended and restated, supplemented or otherwise modified from time to time, the "**Agreement**").

RECITALS

A. WHEREAS, following the execution of this Agreement on May 6, 2016, the parties hereto entered into Amendment No. 1 whereby Lender made available 2018 Term Loan Commitments in respect of a 2018 Term A Loan Advance and a 2018 Term B Loan Advance (in each case as defined below) in an aggregate principal amount of up to Fifty Million Dollars ($50,000,000).

B. WHEREAS, immediately prior to the Second Amendment Closing Date (as defined below), there are 2018 Term Loan Advances outstanding hereunder in the aggregate principal amount of Thirty-Five Million Dollars ($35,000,000) and Lender has not made any 2018 Term B Loan Advance to Borrower.

C. **WHEREAS**, Borrower desires to obtain additional term loan commitments in an aggregate principal amount of One Hundred Million Dollars ($100,000,000) for general corporate purposes permitted pursuant to the terms of this Agreement.

D. **WHEREAS**, the parties hereto desire to further amend this Agreement upon the terms and subject to the conditions set forth herein and in Amendment No. 2 to *inter alia* provide for such additional term loan commitments and to reduce the 2018 Term Loan Commitment to zero ($0).

NOW, THEREFORE, in consideration of the mutual conditions and agreements set forth in this Agreement and the other Loan Documents and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto hereby agree as follows:

DEFINITIONS AND RULES OF CONSTRUCTION

Unless otherwise defined herein, the following capitalized terms shall have the following meanings:

"**2018 End of Term Charge**" shall have the meaning assigned to such term in Section 2.6.

"**2018 Prepayment Charge**" shall have the meaning assigned to such term in Section 2.4.

"**2018 Term A Loan Advance**" shall have the meaning assigned to such term in Section 2.1.1(a).

"**2018 Term B Loan Advance**" shall have the meaning assigned to such term in Section 2.1.1(a).

"**2018 Term Commitment**" means as to any Lender, the obligation of such Lender, if any, to make a 2018 Term Loan Advance to the Borrower in a principal amount not to exceed the amount set forth under the heading "2018 Term Loan Advances" under the heading "Commitment" opposite such Lender's name on Schedule 1.1.

"**2018 Term Loan Advance**" and "**2018 Term Loan Advances**" shall have the meaning assigned to such terms in Section 2.1.1(a).

"**2018 Term Loan Interest Rate**" means for any day, a floating per annum rate equal to the greater of either (a) 8.85%, or (b) the sum of (i) 8.85%, plus (ii) the Prime Rate minus five and one half of one percent (5.50%).

"**2018 Term Loan Maturity Date**" means June 1, 2023.

"**2021 End of Term Charge**" shall have the meaning assigned to such term in Section 2.6.

"**2021 Term Commitment**" means as to any Lender, the obligation of such Lender, if any, to make a 2021 Term Loan Advance to the Borrower in a principal amount not to exceed the amount set forth under the heading "2021 Term Loan Advances" under the heading "Commitment" opposite such Lender's name on Schedule 1.1.

"**2021 Term Loan Advance**" and "**2021 Term Loan Advances**" shall have the meaning assigned to such terms in Section 2.1.2(a).

"**2021 Term Loan Interest Rate**" means for any day, a floating per annum rate equal to the greater of either (a) 8.25%, or (b) the sum of (i) 8.25%, plus (ii) the Prime Rate minus three and one quarter of one percent (3.25%).

"**2021 Term Loan Maturity Date**" means June 1, 2023; provided, however, that if Borrower duly extends the 2021 Term Loan Maturity Date pursuant to Section 2.1.2(e), then the 2021 Term Loan Maturity Date shall mean June 1, 2024 or June 1, 2025, as applicable.

"**Account Control Agreement(s)**" means any agreement entered into by and among Agent, Borrower and a third party bank or other institution (including a Securities Intermediary) in which Borrower maintains a Deposit Account or an account holding Investment Property and which grants Agent a perfected first priority security interest in the subject account or accounts.

"**Accounting Standards**" means accounting principles used by uniQure Holdings in the preparation of its consolidated financial statements for U.S. Securities Exchange Commission filings, being IFRS or GAAP, as applicable.

"**ACH Authorization**" means the ACH Debit Authorization Agreement in substantially the form of Exhibit H.

"**Advance**" means a Term Loan Advance, a 2018 Term Loan Advance or a 2021 Term Loan Advance.

"**Advance Date**" means the funding date of an Advance.

"**Advance Request**" means a request for an Advance submitted by a Borrower to Lender in substantially the form of Exhibit A.

"**Affiliate**" means (a) any Person that directly or indirectly controls, is controlled by, or is under common control with the Person in question, (b) any Person directly or indirectly owning, controlling or holding with power to vote twenty percent (20%) or more of the outstanding voting securities of another Person, (c) any Person twenty percent (20%) or more of whose outstanding voting securities are directly or indirectly owned, controlled or held by another Person with power to vote such securities, or (d) any Person related by blood or marriage to any Person described in subsection (a), (b) or (c) of this paragraph. As used in the definition of "Affiliate," the term "control" means the possession, directly or indirectly, of the power to direct or cause the direction of the management and policies of a Person, whether through ownership of voting securities, by contract or otherwise.

"**Agreement**" has the meaning given to it in the preamble to this Agreement.

"**Amendment No. 1**" has the meaning given to it in the preamble to this Agreement.

"**Amendment No. 2**" has the meaning given to it in the preamble to this Agreement.

"**Anti-Corruption Laws**" shall mean all laws, rules, and regulations of any jurisdiction applicable to Borrower or any of its Affiliates from time to time concerning or relating to bribery or corruption, including without limitation the United States Foreign Corrupt Practices Act of 1977, as amended, the UK Bribery Act 2010 and other similar legislation in any other jurisdictions.

"**Anti-Terrorism Laws**" means any laws, rules, regulations or orders relating to terrorism or money laundering, including without limitation Executive Order No. 13224 (effective September 24, 2001), the USA PATRIOT Act, the laws comprising or implementing the Bank Secrecy Act, and the laws administered by OFAC.

"**Assignee**" has the meaning given to it in Section 11.12.

"**Blocked Person**" means any Person: (a) listed in the annex to, or is otherwise subject to the provisions of, Executive Order No. 13224, (b) a Person owned or controlled by, or acting for or on behalf of, any Person that is listed in the annex to, or is otherwise subject to the provisions of, Executive Order No. 13224, (c) a Person with which any Lender is prohibited from dealing or otherwise engaging in any transaction by any Anti-Terrorism Law, (d) a Person that commits, threatens or conspires to commit or supports "terrorism" as defined in Executive Order No. 13224, or (e) a Person that is named a "specially designated national" or "blocked person" on the most current list published by OFAC or other similar list.

"**Board**" means the supervisory board or the single board of directors of uniQure Holdings in place from time to time.

"**Borrower Products**" means all products, software, service offerings, technical data or technology currently being designed, manufactured or sold by Borrower or which Borrower intends to sell, license, or distribute in the future including any products or service offerings under development, collectively, together with all products, software, service offerings, technical data or technology that have been sold, licensed or distributed by Borrower since its incorporation.

"**Business Day**" is any day other than a Saturday or Sunday, a day on which Lender is closed or a day on which banks are closed for general business in the Netherlands.

"**Cash**" means all cash and liquid funds.

"**Change in Control**" means any (i) reorganization, recapitalization, consolidation or merger (or similar transaction or series of related transactions) of uniQure Holdings or Borrower sale or exchange of outstanding shares (or similar transaction or series of related transactions) of uniQure Holdings' or Borrower's outstanding shares immediately before consummation of such transaction or series of related transactions do not, immediately after consummation of such transaction or series of related transactions, retain shares representing more than fifty percent (50%) of the voting power of the surviving entity of such transaction or series of related

transactions (or the parent of such surviving entity if such surviving entity is wholly owned by such parent), in each case without regard to whether uniQure Holdings or Borrower is the surviving entity, or (ii) sale or issuance by uniQure Holdings or Borrower of new shares of Preferred Securities of uniQure Holdings or Borrower to investors, none of whom are current investors in uniQure Holdings or Borrower, and such new Preferred Securities are senior to all existing Preferred Securities and ordinary shares or common stock of uniQure Holdings or Borrower, as applicable, with respect to liquidation preferences, and the aggregate liquidation preference of such new Preferred Securities is more than fifty percent (50%) of the aggregate liquidation preference of all shares of Preferred Securities of uniQure Holdings or Borrower, as applicable.

"**Collateral**" means the property described in Section 3.

"**Collateral Documents**" means the security documents described in Section 3.

"**Commitment**" means as to any Lender, such Lender's 2018 Term Commitment or 2021 Term Commitment, as the case may be.

"**Confidential Information**" has the meaning given to it in Section 10.11.

"**Contingent Obligation**" means, as applied to any Person, any direct or indirect liability, contingent or otherwise, of that Person with respect to (i) any indebtedness, lease, dividend, letter of credit or other obligation of another, including any such obligation directly or indirectly guaranteed, endorsed, co-made or discounted or sold with recourse by that Person, or in respect of which that Person is otherwise directly or indirectly liable; (ii) any obligations with respect to undrawn letters of credit, corporate credit cards or merchant services issued for the account of that Person; and (iii) all obligations arising under any interest rate, currency or commodity swap agreement, interest rate cap agreement, interest rate collar agreement, or other agreement or arrangement designated to protect a Person against fluctuation in interest rates, currency exchange rates or commodity prices; provided, however, that the term "Contingent Obligation" shall not include endorsements for collection or deposit in the ordinary course of business. The amount of any Contingent Obligation shall be deemed to be an amount equal to the stated or determined amount of the primary obligation in respect of which such Contingent Obligation is made or, if not stated or determinable, the maximum reasonably anticipated liability in respect thereof as determined by such Person in good faith; provided, however, that such amount shall not in any event exceed the maximum amount of the obligations under the guarantee or other support arrangement.

"**continuing**" means, with respect to an Event of Default, an Event of Default that has not been remedied or waived.

"**Copyright License**" means any written agreement granting any right to use any Copyright or Copyright registration, now owned or hereafter acquired by Borrower or in which Borrower now holds or hereafter acquires any interest.

"**Copyrights**" means all copyrights, whether registered or unregistered, held by the Borrower pursuant to the laws of the Netherlands, or of any other country.

"**CSL Licenses**" is defined in the definition of "Permitted Liens".

"**Deposit Accounts**" means any "deposit accounts," including any checking account, savings account, or certificate of deposit and any deposit account as defined in the UCC.

"**End of Term Charge**" means collectively, the charges set forth in Sections 2.5 and 2.6.

"**Equity Interests**" means, with respect to any Person, the capital stock, partnership or limited liability company interest, or other equity securities or equity ownership interests of such Person.

"**Event of Default**" has the meaning given to it in Section 8.

"**Existing 2021 Term Loan Maturity Date**" has the meaning given to it in Section 2.1.2(e).

"**Existing Loan and Security Agreement**" means that certain Amended and Restated Loan and Security Agreement dated as of June 26, 2014 (as the same may have been amended, modified, supplemented or restated and in effect from time to time).

"**Extera Judgment**" means any settlement or judgment in connection with the currently pending dispute with Extera Partners so long as such settlement or judgment is limited to monetary damages and does not exceed $15,000,000 in the aggregate and no payment is made if an Event of Default has occurred and is continuing.

"**Facility Charge**" means one and one-quarter of one percent (1.25%) of the original principal amount of the Term Loan advanced on the Original Closing Date.

"**Financial Statements**" has the meaning given to it in Section 7.1.

"**First Amendment Closing Date**" means December 6, 2018.

"**Funding Documents**" means the following: (i) a certificate of good standing for US Borrower from its state of incorporation and from all other US jurisdictions in which it does business to the extent that the failure to be qualified to do business would have a Material Adverse Effect and for uniQure Bio an extract of its registration in the Trade Register of the Dutch Chamber of Commerce, a copy of the deed of incorporation and, if amended after incorporation, the articles of association currently in force and effect; (ii) completed Schedules and Exhibits to this Agreement; (iii) executed originals of the following: (x) the Account Control Agreements, and any other documents executed in connection with the Secured Obligations or the transactions contemplated hereby, as the same may from time to time be amended, modified, supplemented or restated and (y) the Perfection Certificate; (iv) legal opinion of Lender's counsel; (v) the insurance policies and/or endorsements required pursuant to Section 6.1 hereof; (vi) documents, releases, terminations, and other instruments as may be necessary or proper to release any creditor's Lien in the Intellectual Property of Borrower including, without limitation, UCC financing statement amendments and appropriate filings with any appropriate register or authority in any jurisdiction; and (vii) and all other documents and instruments reasonably required by Lender to effectuate the transactions contemplated hereby or to create and perfect the

Liens of Lender with respect to all Collateral, in all cases in form and substance reasonably acceptable to Lender.

"**GAAP**" means generally accepted accounting principles in the United States of America.

"**IFRS**" are the International Financial Reporting Standards, a collection of guidelines and rules set by the International Accounting Standards Board (www.iasb.org) which are applicable to the circumstances as of the date of determination.

"**Indebtedness**" means indebtedness of any kind, including (a) all indebtedness for borrowed money or the deferred purchase price of property or services (excluding trade credit entered into in the ordinary course of business due within sixty (60) days), including reimbursement and other obligations with respect to surety bonds and letters of credit, (b) all obligations evidenced by notes, bonds, debentures or similar instruments, (c) all capital lease obligations (as such term is understood under GAAP), and (d) all Contingent Obligations.

"**Insolvency Proceeding**" is any proceeding by or against any Person under the Dutch Bankruptcy Act, or any other bankruptcy or insolvency law, including assignments for the benefit of creditors, compositions, extensions generally with its creditors, or proceedings seeking reorganization, arrangement, or other relief.

"**Intellectual Property**" means any and all intellectual property rights in any country or jurisdiction, including but not limited to all of Borrower's Copyrights; Trademarks; Patents; Licenses; trade secrets and inventions; mask works, utility models, layout-designs (topographies) of integrated circuits, know-how, industrial designs, neighboring rights, database rights or other rights in compilations of data, trade names, internet domain names, plant variety rights and any and all rights of a similar nature, either (i) now known, contemplated or unforeseen, (ii) having a statutory basis or existing under equity, common law or otherwise, or (iii) registered, deposited, filed or not, and including any and all rights in connection with applications for or rights to apply for or acquire any and all of such rights.

"**Intra-Group Loans**" means the liabilities owed by any Obligor to any other Obligor.

"**Investment**" means any beneficial ownership (including stock, partnership or limited liability company interests) of or in any Person, or any loan, advance or capital contribution to any Person or the acquisition of all, or substantially all, of the assets of another Person,

"**Joinder Agreements**" means for each Subsidiary, a completed and executed Joinder Agreement in substantially the form attached hereto as Exhibit G.

"**Leasehold Financing**" means any financing entered into by Borrower in respect of improvements of its facilities and/or financed equipment in any location in an aggregate amount of up to $10,000,000.

"**Lender**" has the meaning given to it in the preamble to this Agreement.

"**License**" means any Copyright License, Patent License, Trademark License or other license of rights or interests.

"**Lien**" means any mortgage, deed of trust, pledge, hypothecation, assignment for security, security interest, encumbrance, levy, lien or charge of any kind, whether voluntarily incurred or arising by operation of law or otherwise, against any property, any conditional sale or other title retention agreement, and any lease in the nature of a security interest.

"**Loan Documents**" means this Agreement, the Notes (if any), the ACH Authorization, the Account Control Agreements, any reaffirmations, the Joinder Agreements, all UCC Financing Statements, the Warrant Agreement, any intellectual property security agreement, and any other documents executed in connection with the Secured Obligations or the transactions contemplated hereby, as the same may from time to time be amended, modified, supplemented or restated.

"**Material Adverse Effect**" means a material adverse effect upon: (i) the business, operations, properties, assets or condition (financial or otherwise) of the Obligors, taken as a whole, other than in and of itself (x) the expenditure of cash in the ordinary course, or (y) adverse results of a preclinical or clinical trial or program or the denial, delay or limitation of approval of, or taking of any other regulatory action by, the United States Food and Drug Administration or any other governmental entity with respect to any biologic product or drug; or (ii) the ability of an Obligor to perform the Secured Obligations when due in accordance with the terms of the Loan Documents, or the ability of Lender to enforce any of its rights or remedies with respect to the Secured Obligations; or (iii) the Collateral or Lender's Liens on the Collateral or the priority of such Liens.

"**Maximum 2021 Term Loan Amount**" means an aggregate principal amount of up to One Hundred Million Dollars ($100,000,000).

"**Maximum Rate**" shall have the meaning assigned to such term in Section 2.2.

"**Note(s)**" means a promissory note or promissory notes to evidence an Advance made by a Lender.

"**OFAC**" is the U.S. Department of Treasury Office of Foreign Assets Control.

"**OFAC Lists**" are, collectively, the Specially Designated Nationals and Blocked Persons List maintained by OFAC pursuant to Executive Order No. 13224, 66 Fed. Reg. 49079 (Sept. 25, 2001) and/or any other list of terrorists or other restricted Persons maintained pursuant to any of the rules and regulations of OFAC or pursuant to any other applicable Executive Orders.

"**Ordinary Shares**" means the Ordinary Shares, €1 par value per share, of uniQure Bio.

"**Original Closing Date**" means June 13, 2013.

"**Original Term Loan Advances**" has the meaning given to it in Section 2.1.1(a).

"**Patent License**" means any written agreement granting any right with respect to any invention on which a Patent is in existence or a Patent application is pending, in which agreement Borrower now holds or hereafter acquires any interest.

"**Patents**" means any patent in the Netherlands or in any other country, all registrations and recordings thereof, and all applications for patents of, or rights corresponding thereto, in the Netherlands or any other country.

"**Permitted Convertible Debt**" means Indebtedness of Borrower consisting of one or more series of notes and notes issued in exchange therefor, that are in each case convertible into Ordinary Shares (or other securities or property following a merger event or other change of the Ordinary Shares), or cash or any combination of cash and Ordinary Shares; provided, however, that such Indebtedness shall (a) be either unsecured or Subordinated Indebtedness, (b) not require any mandatory redemption, prepayment, repurchase, "put", "call", or conversion for cash prior to stated maturity other than any customary provision requiring an offer to purchase such notes as a result of a "change of control", fundamental change, delisting or termination of trading or similar provision, (c) mature after, and not require any scheduled amortization or other scheduled payments of principal prior to, the date that is 181 days after the latest 2021 Term Loan Maturity Date (after giving effect to all possible extensions thereof under Section 2.1.2(e)), and (d) not be guaranteed by any Subsidiary of Borrower.

"**Permitted Indebtedness**" means: (i) Indebtedness of Borrower in favor of Lender arising under this Agreement or any other Loan Document; (ii) Indebtedness existing on the Restatement Date which is disclosed in Schedule 1A; (iii) Indebtedness of up to $250,000 outstanding at any time secured by a Lien described in clause (vii) of the defined term "Permitted Liens," provided such Indebtedness does not exceed the lesser of the cost or fair market value of the equipment financed with such Indebtedness; (iv) Indebtedness to trade creditors incurred in the ordinary course of business, including Indebtedness incurred in the ordinary course of business with corporate credit cards; (v) Indebtedness that also constitutes a Permitted Investment; (vi) Subordinated Indebtedness; (vii) reimbursement obligations in connection with letters of credit that are secured by cash or cash equivalents and issued on behalf of the Borrower or a Subsidiary thereof in an amount not to exceed $200,000 at any time outstanding, (viii) the Leasehold Financing; (ix) any contingent consideration payable in connection with the acquisition of InoCard in an amount not to exceed €15,000,000 in accordance with the term of the Sale and Purchase Agreement dated as of July 15, 2014 by any among Prof. Hugo Katus, Prof. Patrick Most, uniQure Holdings and uniQure Bio (as amended from time to time) (provided however, no cash payments may be made if an Event of Default has occurred and is continuing); (x) any operating leases; (xi) any Intra-Group Loans; (xii) any liability arising pursuant to any guarantee in the form of a declaration of joint and several liability (*hoofdelijke aansprakelijkheid*) as referred to in article 2:403 Dutch civil code in respect of a member of the group and any residual liability with respect to such declaration arising pursuant to article 2:404 Dutch civil code; (xiii) any joint and several liability arising as a result of (the establishment) of a fiscal unity (*fiscale eenheid*) between members of the group incorporated in the Netherlands; (xiv) Permitted Convertible Debt not to exceed Five Hundred Million Dollars ($500,000,000) in aggregate principal amount at any time outstanding; (xv) other Indebtedness in an aggregate amount not to exceed $100,000 at any time outstanding, and (xvi) extensions, refinancings and renewals of any items of Permitted Indebtedness, provided that the principal amount is not

increased or the terms modified to impose materially more burdensome terms upon Borrower or its Subsidiary, as the case may be.

"**Permitted Investment**" means: (i) Investments existing on the Restatement Date which are disclosed in Schedule 1B; (ii) (a) marketable direct obligations issued or unconditionally guaranteed by any agency or any country thereof maturing within two-years from the date of acquisition thereof, (b) commercial paper maturing no more than two-years from the date of creation thereof and currently having a rating of at least A-2 or P-2 from either Standard & Poor's Corporation or Moody's Investors Service, (c) certificates of deposit issued by any bank with assets of at least $500,000,000 maturing no more than two-years from the date of investment therein, and (d) money market accounts; (iii) repurchases of stock from former employees, directors, or consultants of Borrower under the terms of applicable repurchase agreements at the original issuance price of such securities in an aggregate amount not to exceed $500,000 in any fiscal year, provided that no Event of Default has occurred, is continuing or would exist after giving effect to the repurchases; (iv) Investments accepted in connection with Permitted Transfers; (v) Investments (including debt obligations) received in connection with the bankruptcy or reorganization of customers or suppliers and in settlement of delinquent obligations of; and other disputes with, customers or suppliers arising in the ordinary course of Borrower's business; (vi) Investments consisting of notes receivable of, or prepaid royalties and other credit extensions, to customers and suppliers who are not affiliates, in the ordinary course of business, provided that this subparagraph (vi) shall not apply to Investments of Borrower in any Subsidiary; (vii) Investments consisting of loans not involving the net transfer on a substantially contemporaneous basis of cash proceeds to employees, officers or directors relating to the purchase of capital stock of Borrower pursuant to employee stock purchase plans or other similar agreements approved by the Board; (viii) Investments consisting of employee travel advances, employee relocation loans and other employee loans and advances in the ordinary course of business; (ix) Investments in newly-formed Subsidiaries organized in the Netherlands or any other country, provided that such Subsidiaries enter into a Joinder Agreement promptly after their formation by Borrower and execute such other documents as shall be reasonably requested by Lender; (x) joint ventures or strategic alliances in the ordinary course of Borrower's business consisting of the nonexclusive licensing of technology, the development of technology or the providing of technical support; (xi) any Intra-Group Loans; and (xii) other Investments that do not exceed $1,000,000 in the aggregate.

"**Permitted Liens**" means any and all of the following: (i) Liens in favor of Lender; (ii) Liens existing on the Second Amendment Closing Date which are disclosed in Schedule 1C; (iii) Liens for taxes, fees, assessments or other governmental charges or levies, either not delinquent or being contested in good faith by appropriate proceedings; provided, that Borrower maintains adequate reserves therefor in accordance with Accounting Standards; (iv) Liens securing claims or demands of materialmen, artisans, mechanics, carriers, warehousemen, landlords and other like Persons arising in the ordinary course of Borrower's business and imposed without action of such parties; provided, that the payment thereof is not yet required; (v) Liens arising from judgments, decrees or attachments in circumstances which do not constitute an Event of Default hereunder; (vi) the following deposits, to the extent made in the ordinary course of business: deposits under worker's compensation, unemployment insurance, social security and other similar laws, or to secure the performance of bids, tenders or contracts (other than for the repayment of borrowed money) or to secure indemnity, performance or other

similar bonds for the performance of bids, tenders or contracts (other than for the repayment of borrowed money) or to secure statutory obligations (other than liens arising under environmental liens) or surety or appeal bonds, or to secure indemnity, performance or other similar bonds; (vii) Liens on equipment or software or other intellectual property constituting purchase money liens and liens in connection with capital leases securing Indebtedness permitted in clause (iii) of "Permitted Indebtedness"; (viii) Liens incurred in connection with Subordinated Indebtedness; (ix) leasehold interests in leases or subleases and licenses granted in the ordinary course of business and not interfering in any material respect with the business of the licensor; (x) Liens in favor of customs and revenue authorities arising as a matter of law to secure payment of custom duties that are promptly paid on or before the date they become due; (xi) Liens on insurance proceeds securing the payment of financed insurance premiums that are promptly paid on or before the date they become due (provided that such Liens extend only to such insurance proceeds and not to any other property or assets); (xii) statutory and common law rights of set-off and other similar rights as to deposits of cash and securities in favor of banks, other depository institutions and brokerage firms and any Lien, netting or set-off arrangement granted or entered into by any Obligor under or in connection with the ordinary banking arrangements of such Obligor as a result of the applicable general terms and conditions of the relevant account bank where the Obligor maintains a bank account (including, in respect of an account bank in the Netherlands, the general banking terms and conditions (*algemene bankvoorwaarden*)); (xiii) easements, zoning restrictions, rights-of-way and similar encumbrances on real property imposed by law or arising in the ordinary course of business so long as they do not materially impair the value or marketability of the related property; (xiv) Liens on cash or cash equivalents securing obligations permitted under clause (vii) of the definition of Permitted Indebtedness; (xv) Liens incurred in connection with the Leasehold Financing which are limited to the improvements and equipment financed in respect of Borrower's property located thereon; (xvi) licenses granted by Borrower or its affiliates pursuant to the terms of that certain Commercialization and License Agreement, dated June 24, 2020, by and between uniQure Bio and CSL Berhing LLC, as amended and in effect from time to time (the "**CSL Licenses**"); and (xvii) Liens incurred in connection with the extension, renewal or refinancing of the indebtedness secured by Liens of the type described in clauses (i) through (xi) and (xv) above; provided, that any extension, renewal or replacement Lien shall be limited to the property encumbered by the existing Lien and the principal amount of the indebtedness being extended, renewed or refinanced (as may have been reduced by any payment thereon) does not increase.

"**Permitted Transfers**" means (i) sales of inventory in the normal course of business; (ii) exclusive licenses and similar arrangements for the use of Intellectual Property in the ordinary course of business that could not result in a legal transfer of title of the licensed property; (iii) dispositions of worn-out, obsolete or surplus equipment that is, in the reasonable judgment of Borrower, no longer economically practicable to maintain or useful in the ordinary course of business of Borrower; (iv) other Transfers of assets having a fair market value of not more than $250,000 in the aggregate in any fiscal year; (v) the entering into of commercialization, co-development or license agreements with development or collaboration partners in the ordinary course of business; and (vi) the CSL Licenses.

"**Person**" means any individual, sole proprietorship, partnership, joint venture, trust, unincorporated organization, association, corporation, limited liability company, institution, other entity or government.

"**Preferred Securities**" means at any given time any equity issued by uniQure Holdings or Borrowers, as applicable, that has any rights, preferences or privileges senior to uniQure Holdings' or Borrower' ordinary shares or common stock, as applicable.

"**Prime Rate**" means the "prime rate" as reported in *The Wall Street Journal*, and if not reported, then the prime rate most recently reported in *The Wall Street Journal*.

"**Restatement Date**" shall mean May 6, 2016.

"**Sanctioned Country**" shall mean, at any time, a country or territory which is the subject or target of any Sanctions.

"**Sanctioned Person**" shall mean, at any time, (a) any Person listed in any Sanctions-related list of designated Persons maintained by the Office of Foreign Assets Control of the U.S. Department of the Treasury or the U.S. Department of State, or by the United Nations Security Council, the European Union or any EU member state, (b) any Person operating, organized or resident in a Sanctioned Country or (c) any Person controlled by any such Person.

"**Sanctions**" shall mean economic or financial sanctions or trade embargoes imposed, administered or enforced from time to time by (a) the U.S. government, including those administered by the Office of Foreign Assets Control of the U.S. Department of the Treasury or the U.S. Department of State, or (b) the United Nations Security Council, the European Union or Her Majesty's Treasury of the United Kingdom.

"**Second Advance End of Term Charge**" is defined in Section 2.6.

"**Second Amendment Closing Date**" means January 29, 2021.

"**Secured Obligations**" means Borrower's obligations under this Agreement and any Loan Document, including any obligation to pay any amount now owing or later arising.

"**Subordinated Indebtedness**" means Indebtedness subordinated to the Secured Obligations in amounts and on terms and conditions satisfactory to Lender in its sole discretion.

"**Subsequent Financing**" means any equity financing involving the sale and issuance of Borrower's Equity Interests that is broadly marketed to multiple investors and consummated after the Second Amendment Closing Date, provided, however, that in no event shall the sale and issuance of Borrower's Equity Interests in any "at-the-market offering" (as defined in Rule 415 promulgated under the Securities Act of 1933, as amended) be deemed a "Subsequent Financing".

"**Subsidiary**" means an entity, whether corporate, partnership, limited liability company, joint venture or otherwise, in which uniQure Holdings owns or controls directly or indirectly 50% or more of the outstanding voting securities, including each entity listed on Schedule 1 hereto.

"**Term Loan**" shall mean the term loans in an aggregate principal amount of up to Fifty Million Dollars ($50,000,000) made available under this Agreement as described in Section 2.1.1.

"**Term Loan Advance**" means an advance of a Term Loan by a Lender to Borrower pursuant to this Agreement.

"**Term Loan Maturity Date**" means May 1, 2020.

"**Third Advance Facility Charge**" means 0.75% of the original principal amount of the aggregate principal amount of the Term Loans advanced pursuant to the Loan Documents.

"**Trademark License**" means any written agreement granting any right to use any Trademark or Trademark registration, now owned or hereafter acquired by Borrower or in which Borrower now holds or hereafter acquires any interest.

"**Trademarks**" means all trademarks (registered, common law or otherwise) and any applications in connection therewith, including registrations, recordings and applications with any appropriate register or authority in any jurisdiction.

"**UCC**" means the Uniform Commercial Code as the same is, from time to time, in effect in the State of California; provided, that in the event that, by reason of mandatory provisions of law, any or all of the attachment, perfection or priority of, or remedies with respect to, Lender's Lien on any Collateral is governed by the Uniform Commercial Code as the same is, from time to time, in effect in a jurisdiction other than the State of California, then the term "UCC" shall mean the Uniform Commercial Code as in effect, from time to time, in such other jurisdiction solely for purposes of the provisions thereof relating to such attachment, perfection, priority or remedies and for purposes of definitions related to such provisions.

"**Warrant Agreement**" means the Warrant Agreement dated as of September 20, 2013 by and between uniQure Holdings and Hercules Capital, Inc. (formerly known as Hercules Technology Growth Capital, Inc.).

Unless otherwise specified, all references in this Agreement or any Annex or Schedule hereto to a "Section," "subsection," "Exhibit," "Annex," or "Schedule" shall refer to the corresponding Section, subsection, Exhibit, Annex, or Schedule in or to this Agreement. Unless otherwise specifically provided herein, any accounting term used in this Agreement or the other Loan Documents shall have the meaning customarily given such term in accordance with Accounting Standards, and all financial computations hereunder shall be computed in accordance with Accounting Standards, consistently applied. Unless otherwise defined herein or in the other Loan Documents, terms that are used herein or in the other Loan Documents and defined in the UCC shall have the meanings given to them in the UCC.

THE LOANS

Reserved.

2018 Term Loan.

(a) First Amendment Closing Date. Pursuant to the transactions described in this Agreement as amended by Amendment No. 1, on the First Amendment Closing Date, Twenty Million Dollars ($20,000,000) of the principal amount of the Original Term Loan Advances was deemed to constitute and refer to, and was converted into, the 2018 Term A Loan Advance hereunder, without constituting a novation. Such conversion of the Original Term Loan Advances into the 2018 Term A Loan Advance hereunder was deemed an Advance on the First Amendment Closing Date for purposes of this Agreement. In furtherance thereof, the Lenders severally (and not jointly) made, in an amount not exceeding their respective 2018 Term Commitment as in effect on the First Amendment Closing Date, and Borrower agreed to draw, one (1) 2018 Term Loan Advance in an aggregate principal amount of Thirty-Five Million Dollars ($35,000,000) (inclusive of the Original Term Loan Advances) on the First Amendment Closing Date (the "2018 Term A Loan Advance"). Furthermore, pursuant to the transactions described in this Agreement as amended by Amendment No. 1, on the First Amendment Closing Date, Lender provided severally (and not jointly) its respective 2018 Term Commitment to make one (1) 2018 Term Loan Advance in a principal amount of Fifteen Million Dollars ($15,000,000) (the "2018 Term B Loan Advance", and together with the 2018 Term A Loan Advance, the "2018 Term Loan Advances").

Outstanding Principal Amount; Termination of Commitments. The parties hereto acknowledge and agree that as of the Second Amendment Closing Date: (i) Lender has not made any 2018 Term B Loan Advance to Borrower, (ii) the aggregate outstanding principal amount of the 2018 Term Loan Advances is Thirty-Five Million Dollars ($35,000,000) and (iii) Borrower shall not be permitted to draw, and Lender shall not make, any further 2018 Term Loan Advances.

Interest. The principal balance of each 2018 Term Loan Advance shall bear interest thereon from such Advance Date at the 2018 Term Loan Interest Rate based on a year consisting of 360 days, with interest computed daily based on the actual number of days elapsed. The 2018 Term Loan Interest Rate will float and change on the day the Prime Rate changes from time to time.

Payment. Borrower will pay interest on each 2018 Term Loan Advance on the first (1st) Business Day of each month, beginning the month after the Advance Date. The entire 2018 Term Loan Advances principal balance and all accrued but unpaid interest thereon hereunder, shall be due and payable on the 2018 Term Loan Maturity Date. Borrower shall make all payments under this Agreement without setoff, recoupment or deduction and regardless of any counterclaim or defense. Lender will initiate debit entries to the Borrower's account as authorized on the ACH Authorization on each payment date of all periodic obligations payable to Lender under each 2018 Term Loan Advance. Once repaid, the 2018 Term Loan Advances or any portion thereof may not be reborrowed.

1.1.2 2021 Term Loan.

(a) 2021 Term Loan Advances. Subject to the terms and conditions of this Agreement, the Lenders agree severally (and not jointly) to make, in an amount not to exceed

their respective 2021 Term Commitment, at the Borrower's request in accordance with clause (b) below, (i) one (1) term loan in an aggregate principal amount of Thirty-Five Million Dollars ($35,000,000) on the Second Amendment Closing Date and (ii) after the Second Amendment Closing Date but on or prior to December 15, 2021, additional term loans in an aggregate principal amount not to exceed Sixty-Five Million Dollars ($65,000,000) (each advance of the term loans referred to in Section 2.1.2(a)(i) or (ii), a "2021 Term Loan Advance" and collectively, the "2021 Term Loan Advances"). The amount of any proposed 2021 Term Loan Advance pursuant to Section 2.1.2(a)(ii) must be a minimum amount of Twenty Million Dollars ($20,000,000). Only one 2021 Term Loan Advance may be requested in each Advance Request and the aggregate outstanding 2021 Term Loan Advances shall not exceed the Maximum 2021 Term Loan Amount. Proceeds of each 2021 Term Loan Advance shall be deposited into an account that is subject to a first priority perfected security interest in favor of Agent perfected by an Account Control Agreement.

Advance Request. To obtain a 2021 Term Loan Advance, Borrower shall complete, sign and deliver an Advance Request (at least (i) in the case of any 2021 Term Loan Advance to be advanced under Section 2.1.2(a)(i), one (1) Business Day before the Advance Date, and (ii) in the case of any 2021 Term Loan Advance to be advanced under Section 2.1.2(a)(ii), at least five (5) Business Days before the Advance Date) to Agent. Lender shall fund its ratable portion of each 2021 Term Loan Advance in the manner requested by the Advance Request provided that each of the conditions precedent to such 2021 Term Loan Advance is satisfied as of the requested Advance Date.

Interest. The principal balance of each 2021 Term Loan Advance shall bear interest thereon from such Advance Date at the 2021 Term Loan Interest Rate based on a year consisting of 360 days, with interest computed daily based on the actual number of days elapsed. The 2021 Term Loan Interest Rate will float and change on the day the Prime Rate changes from time to time.

Payment. Borrower will pay interest on each 2021 Term Loan Advance on the first (1st) Business Day of each month, beginning the month after the Advance Date. The entire 2021 Term Loan Advances principal balance and all accrued but unpaid interest thereon hereunder, shall be due and payable on the 2021 Term Loan Maturity Date. Borrower shall make all payments under this Agreement without setoff, recoupment or deduction and regardless of any counterclaim or defense. Lender will initiate debit entries to the Borrower's account as authorized on the ACH Authorization on each payment date of all periodic obligations payable to Lender under each 2021 Term Loan Advance. Once repaid, the 2021 Term Loan Advances or any portion thereof may not be reborrowed.

Extension of 2021 Term Loan Maturity Date.

(i) Subject to the terms and conditions set forth in clause (ii) below, Borrower may give Agent written notice not later than the date that is thirty (30) days prior to the 2021 Term Loan Maturity Date then in effect hereunder (such 2021 Term Loan Maturity Date then in effect, the "Existing 2021 Term Loan Maturity Date"), that it has elected to extend the 2021 Term Loan Maturity Date by an additional twelve (12) months from the Existing 2021 Term Loan Maturity Date; provided that Borrower may deliver only two (2) such notices of

extension so that the total number of months by which the 2021 Term Loan Maturity Date may be extended under this Section 2.1.2(e) shall not exceed twenty-four (24).

(ii) Notwithstanding the foregoing, no extension of the 2021 Term Loan Maturity Date pursuant to this Section 2.1.2(e) shall be effective unless:

(A) immediately prior to and upon giving effect to such extension (1) the representations and warranties contained in the Loan Documents are true, accurate and complete in all material respects except to the extent such representations and warranties relate to an earlier date, in which case they are true and correct in all material respects as of such date (in all cases without giving effect to any standard(s) of materiality contained in such Loan Documents as to such representations and warranties), (2) no fact or condition exists that would (or would, with the passage of time, the giving of notice, or both) constitute an Event of Default and (3) no event that has had or could reasonably be expected to have a Material Adverse Effect has occurred and is continuing; and

(B) Agent shall have received, without limitation, such other documents, agreements, certificates, notices, reports, filings, opinions, financial statements and other writings reasonably requested by Agent in connection therewith.

Maximum Interest. Notwithstanding any provision in this Agreement or any other Loan Document, it is the parties' intent not to contract for, charge or receive interest at a rate that is greater than the maximum rate permissible by law that a court of competent jurisdiction shall deem applicable hereto (which under the laws of the State of California shall be deemed to be the laws relating to permissible rates of interest on commercial loans) (the "**Maximum Rate**"). If a court of competent jurisdiction shall finally determine that Borrower has actually paid to Lender an amount of interest in excess of the amount that would have been payable if all of the Secured Obligations had at all times borne interest at the Maximum Rate, then such excess interest actually paid by Borrower shall be applied as follows: first, to the payment of the Secured Obligations consisting of the outstanding principal of the Term Loan Advances, the 2018 Term Loan Advances and the 2021 Term Loan Advances; second, after all principal is repaid, to the payment of Lender's accrued interest, costs, expenses, professional fees and any other Secured Obligations; and third, after all Secured Obligations are repaid, the excess (if any) shall be refunded to Borrower.

Default Interest. In the event any payment is not paid on the scheduled payment date, an amount equal to five percent (5%) of the past due amount shall be payable on demand. In addition, upon the occurrence and during the continuation of an Event of Default hereunder, all Secured Obligations, including principal, interest, compounded interest, and professional fees, shall bear interest at a rate per annum equal to the rate set forth in Section 2.1(d), plus five percent (5%) per annum. In the event any interest is not paid when due hereunder, delinquent interest shall be added to principal and shall bear interest on interest, compounded at the rate set forth in Section 2.1(d).

Prepayment. At its option, Borrower may prepay the whole or part (but in an amount not less than $10,000,000 or less if the applicable amount of outstanding Advances are less than $10,000,000 at such time) of:

Upon at least five (5) Business Days prior written notice to Agent, the outstanding 2018 Term Loan Advances including all accrued and unpaid interest thereon, all unpaid Lender's fees and expenses accrued to the date of the repayment (including, without limitation, the Third Advance End of Term Charge and the 2018 End of Term Charge) together with a prepayment charge equal to the following percentage of the amount of the 2018 Term Loan Advances being prepaid: if such 2018 Term Loan Advance amounts are prepaid in any of the first twelve (12) months following the First Amendment Closing Date, two percent (2%); after twelve (12) months following the First Amendment Closing Date but prior to twenty four (24) months following the First Amendment Closing Date, one and one half percent (1.5%); and after twenty four (24) months following the First Amendment Closing Date but prior to the 2018 Term Loan Maturity Date, one percent (1%) (each, a "2018 Prepayment Charge"). Borrower agrees that the 2018 Prepayment Charge is a reasonable calculation of Lender's lost profits in view of the difficulties and impracticality of determining actual damages resulting from an early repayment of the 2018 Term Loan Advances. For the avoidance of doubt, Lender and Agent agree that the 2018 Term A Loan Advances made hereunder does not constitute prepayment of the Original Term Loan Advances.

Upon at least thirty (30) days prior written notice to Agent and only after the date is six months after the Second Amendment Closing Date, the outstanding 2021 Term Loan Advances including all accrued and unpaid interest thereon, all unpaid Lender's fees and expenses accrued to the date of the repayment (including, without limitation, the 2021 End of Term Charge).

Upon the occurrence of a Change in Control, Borrower shall immediately prepay the aggregate outstanding amount of all principal of all Advances and accrued interest thereon through the prepayment date and all unpaid Lender's fees and expenses accrued to the date of the prepayment (including, without limitation, the Third Advance End of Term Charge, the 2018 End of Term Charge and the 2021 End of Term Charge) together with a 2018 Prepayment Charge.

Original End of Term Charge. On the earliest to occur of (i) October 1, 2016, (ii) the date that Borrower prepays the outstanding Secured Obligations, or (iii) the date that the Secured Obligations become due and payable, Borrower shall pay Lender a charge equal to $345,000. Notwithstanding the required payment date of such charge, it shall be deemed earned by Lender as of the Original Closing Date.

Additional End of Term Charges.

On the earliest to occur of (i) June 30, 2018, (ii) the date that Borrower prepays the outstanding Secured Obligations, or (iii) the date that the Secured Obligations become due and payable, Borrower shall immediately pay Lender an additional charge equal to $250,000 (the "**Second Advance End of Term Charge**"). Notwithstanding the required payment date of such charge, it shall be deemed earned by Lender as of June 26, 2014.

On the earliest to occur of (i) the Term Loan Maturity Date, (ii) the date that Borrower prepays the outstanding Secured Obligations in full, or (iii) the date that the Secured Obligations become due and payable, Borrower shall immediately pay Lender an additional charge equal to $970,000 (the "**Third Advance End of Term Charge**"). Notwithstanding the

required payment date of such charge, it shall be deemed earned by Lender as of the Restatement Date.

On the earliest to occur of (i) the 2018 Term Loan Maturity Date, (ii) the date that Borrower prepays the outstanding Secured Obligations in full, or (iii) the date that the Secured Obligations become due and payable, Borrower shall immediately pay Lender One Million Seven Hundred Thirty-Two Thousand Five Hundred Dollars ($1,732,500) (the "**2018 End of Term Charge**"). Notwithstanding the required payment date of such charge, the 2018 End of Term Charge shall be deemed earned by Lender as of the First Amendment Closing Date.

On the earliest to occur of (i) the 2021 Term Loan Maturity Date, (ii) the date that Borrower prepays the outstanding Secured Obligations in respect of the 2021 Term Loan Advances in full, or (iii) the date that the Secured Obligations become due and payable, Borrower shall immediately pay Lender with respect to the 2021 Term Loan Advances a charge equal to following percentages multiplied by the aggregate original principal amount of all 2021 Term Loan Advances extended by Lender (the "**2021 End of Term Charge**"): (A) 1.65% if the date such payment is required to be made occurs after six (6) months following the Second Amendment Closing Date but prior to nine (9) months following the Second Amendment Closing Date, (B) 2.25% if the date such payment is required to be made occurs after nine (9) months following the Second Amendment Closing Date but prior to twelve (12) months following the Second Amendment Closing Date, (C) 3.85% if the date such payment is required to be made occurs after twelve (12) months following the Second Amendment Closing Date but prior to twenty-four (24) months following the Second Amendment Closing Date and (4) 4.85% if the date such payment is required to be made occurs after twenty-four (24) months following the Second Amendment Closing Date; provided, however that immediately upon the effectiveness of each separate twelve (12) month extension of the 2021 Term Loan Maturity Date pursuant to Section 2.1.2(e), each of the foregoing percentages shall be increased by one percent (1%). For the avoidance of doubt, if the 2021 Term Loan Maturity Date is extended twice under Section 2.1.2(e), then each of the foregoing percentages used to calculate the 2021 End of Term Charge shall be increased by two percent (2%) in total. Notwithstanding the required payment date of such charge, the 2021 End of Term Charge shall be deemed earned by Lender, as to such 2021 Term Loan Advance, as of each date a 2021 Term Loan Advance is made.

Notes. If so requested by Lender by written notice to Borrower, then Borrower shall execute and deliver to Lender (and/or, if applicable and if so specified in such notice, to any person who is an assignee of Lender pursuant to Section 11.12) (promptly after the Borrower's receipt of such notice) a Note or Notes to evidence an Advance made by a Lender.

Commitment Fee; Facility Charge. The parties acknowledge and agree that Borrower paid to Lender (i) a commitment fee of $45,000 on or before the Original Closing Date, and such commitment fee was fully earned on the Original Closing Date and non-refundable regardless of the early termination of this Agreement, (ii) the Facility Charge of $125,000 on the Original Closing Date, and that such Facility Charge was fully earned on the Original Closing Date and non-refundable regardless of the early termination of this Agreement, (iii) the facility charge of $200,000 on June 26, 2014, and such facility charge was fully earned on June 26, 2014 and non-refundable regardless of the early termination of this Agreement, (iv) the Third Advance Facility

Charge of $150,000 on the Restatement Date, and such facility charge was fully earned on the Restatement Date and non-refundable regardless of the early termination of this Agreement, (v) the facility charge of $175,000 on the First Amendment Closing Date, and such facility charge was fully earned on the First Amendment Closing Date and non-refundable regardless of the early termination of this Agreement and (vi) the facility charge of $350,000 on the Second Amendment Closing Date, and such facility charge was fully earned on the Second Amendment Closing Date and non-refundable regardless of the early termination of this Agreement.

Pro Rata Treatment. Each payment (including prepayment) on account of any fee and any reduction of the 2018 Term Loan Advances shall be made pro rata according to the 2018 Term A Loan Advance of the relevant Lender. Each payment (including prepayment) on account of any fee and any reduction of the 2021 Term Loan Advances shall be made pro rata according to such 2021 Term Loan Advance of the relevant Lender.

SECURITY INTEREST

As security for the prompt, complete and indefeasible payment when due (whether on the payment dates or otherwise) of all the Secured Obligations:

uniQure Holdings grants to Lender a first ranking right of pledge on its shares in uniQure Bio and uniQure IP;

uniQure Bio grants to Lender a first ranking right of pledge on its shares in its Dutch subsidiaries identified on the Schedule 1 hereto and a security interest in 100% of the capital stock of US Borrower;

Obligor (excluding US Borrower) grants to Lender a first ranking right of pledge on its (a) trade, intercompany and insurance receivables; (b) movable assets and (c) Deposit Accounts; and

US Borrower grants to Lender a security interest in all of US Borrower's right, title, and interest in and to the following personal property whether now owned or hereafter acquired: (a) receivables; (b) equipment; (c) fixtures; (d) general intangibles (except as described below); (e) inventory; (f) Investment Property; (g) Deposit Accounts; (h) Cash; (i) Goods; and all other tangible and intangible personal property of US Borrower whether now or hereafter owned or existing, leased, consigned by or to, or acquired by, US Borrower and wherever located, and any of US Borrower's property in the possession or under the control of Lender; and, to the extent not otherwise included, all proceeds of each of the foregoing and all accessions to, substitutions and replacements for, and rents, profits and products of each of the foregoing, (a), (b), (c) and (d) collectively, the "**Collateral**".

Notwithstanding anything in this Agreement or any other Loan Document to the contrary, in no event shall the Collateral include, and the Obligor shall not be deemed to have granted a security interest in: (i) Intellectual Property; provided, however, that the Collateral shall include all accounts and general intangibles that consist of rights to payment and proceeds from the sale, licensing or disposition of all or any part, or rights in, the Intellectual Property (the "Rights to Payment"); or (ii) any of the Borrower's rights or interests in or under, any license, contract, permit, instrument, security or franchise to which the Borrower is a party or any of its rights or

interests thereunder to the extent, but only to the extent, that such a grant would, under the terms of such license, contract, permit, instrument, security or franchise, result in a breach of the terms of, or constitute a default under, such license, contract, permit, instrument, security or franchise (other than to the extent that any such term would be rendered ineffective pursuant to the UCC or any other applicable law (including the Dutch and the United States Bankruptcy Code) or principles of equity); provided, that immediately upon the ineffectiveness, lapse or termination of any such provision the Collateral shall include, and the Borrower shall be deemed to have granted a security interest in, all the rights and interests described in the foregoing clause (ii) as if such provision had never been in effect. Notwithstanding the foregoing, if a judicial authority (including a U.S. Bankruptcy Court) holds that a security interest in the underlying Intellectual Property is necessary to have a security interest in the Rights to Payment, then the Collateral shall automatically, and effective as of the date of this Agreement, include the Intellectual Property to the extent necessary to permit perfection of Lender's security interest in the Rights to Payment.

CONDITIONS PRECEDENT TO ADVANCES

The obligation of Lender to make the 2021 Term Loan Advances hereunder is subject to the satisfaction by Borrower of the following conditions:

Closing Documents. On or prior to the Advance of the 2021 Term Loan Advances under Section 2.1.2(a)(i) only, Borrower shall have delivered to Lender each of the documents, certificates and other items required pursuant to Section 4 of the Amendment No. 2 and satisfaction of all conditions precedent thereto.

Advance Request. Borrower shall have delivered to Lender the following: (a) an Advance Request for the relevant Advance as required by 2.1.2(b), duly executed by uniQure Holdings' Chief Executive Officer, Chief Financial Officer or Chief Accounting Officer and (b) any other documents Lender may reasonably request.

Other conditions to Advances.

The representations and warranties set forth in this Agreement and in Section 5 shall be true and correct in all material respects on and as of the relevant Advance Date with the same effect as though made on and as of such date, except to the extent such representations and warranties expressly relate to an earlier date.

Borrower shall be in compliance with all the terms and provisions set forth herein and in each other Loan Document on its part to be observed or performed.

The Advance Request shall be deemed to constitute a representation and warranty by Borrower on the relevant Advance Date as to the matters specified in Section 4.4 and as to the matters set forth in the Advance Request.

No Default. As of the relevant Advance Date, (i) no fact or condition exists that would (or would, with the passage of time, the giving of notice, or both) constitute an Event of Default and (ii) no event that has had or could reasonably be expected to have a Material Adverse Effect has occurred and is continuing.

REPRESENTATIONS AND WARRANTIES OF BORROWER

Borrower represents and warrants that:

Corporate Status. uniQure Bio is a private limited liability company duly incorporated and existing under the laws of the Netherlands, and is duly qualified as a foreign corporation in all jurisdictions in which the nature of its business or location of its properties require such qualifications and where the failure to be qualified could reasonably be expected to have a Material Adverse Effect. uniQure Bio's present name, former names (if any), locations, place of formation, tax identification number, organizational identification number and other information are correctly set forth in Exhibit C, as may be updated by uniQure Bio in a written notice (including any Compliance Certificate) provided to Lender after the Restatement Date. US Borrower is a corporation duly organized, legally existing and in good standing under the laws of the State of Delaware, and is duly qualified as a foreign corporation in all jurisdictions in which the nature of its business or location of its properties require such qualifications and where the failure to be qualified could reasonably be expected to have a Material Adverse Effect.

Collateral. The relevant Obligor owns the Collateral and the Intellectual Property, free of all Liens, except for Permitted Liens. Each Obligor has the power and authority to grant to Lender a Lien in the Collateral as security for the Secured Obligations.

Consents. Borrower's execution, delivery and performance of the Notes (if any), this Agreement and all other Loan Documents, (i) have been duly authorized by all necessary corporate action of Borrower, (ii) will not result in the creation or imposition of any Lien upon the Collateral, other than Permitted Liens and the Liens created by this Agreement and the other Loan Documents, (iii) do not violate any provisions of Borrower's articles of association, or any, law, regulation, order, injunction, judgment, decree or writ to which Borrower is subject and (iv) except as described on Schedule 5.3, do not violate any contract or agreement or require the consent or approval of any other Person which has not already been obtained. The individual or individuals executing the Loan Documents are duly authorized to do so.

Material Adverse Effect. No event that has had or could reasonably be expected to have a Material Adverse Effect has occurred and is continuing. Borrower is not aware of any event likely to occur that is reasonably expected to result in a Material Adverse Effect.

Actions Before Governmental Authorities. Except as described on Schedule 5.5, there are no actions, suits or proceedings at law or in equity or by or before any governmental authority now pending or, to the knowledge of uniQure Holdings, threatened against or affecting Borrower or its property (i) which seek to prevent, enjoin, hinder or delay the transactions contemplated by the Loan Documents or (ii) as to which there is a reasonable possibility of an adverse determination and which, if adversely determined, would reasonably be expected to, individually or in the aggregate, have a Material Adverse Effect on Borrower's business.

Laws. Borrower, to its knowledge, is not in violation of any law, rule or regulation, or in default with respect to any judgment, writ, injunction or decree of any governmental authority, where such violation or default is reasonably expected to result in a Material Adverse Effect. Borrower, to its knowledge, is not in default in any manner under any provision of any

agreement or instrument evidencing indebtedness, or any other material agreement to which it is a party or by which it is bound and for which such default would reasonably be expected to have a Material Adverse Effect on Borrower's business.

Neither Borrower nor any of its Subsidiaries is an "investment company" or a company "controlled" by an "investment company" under the Investment Company Act of 1940, as amended, as applicable. Neither Borrower nor any of its Subsidiaries is engaged as one of its important activities in extending credit for margin stock (under Regulations X, T and U of the Federal Reserve Board of Governors, as applicable). Borrower and each of its Subsidiaries has complied in all material respects with the Federal Fair Labor Standards Act, as applicable. Neither Borrower nor any of its Subsidiaries is a "holding company" or an "affiliate" of a "holding company" or a "subsidiary company" of a "holding company" as each term is defined and used in the Public Utility Holding Company Act of 2005, as applicable. Neither Borrower's nor any of its Subsidiaries' properties or assets has been used by Borrower or such Subsidiary or, to Borrower's knowledge, by previous Persons, in disposing, producing, storing, treating, or transporting any hazardous substance other than in material compliance with applicable laws. Borrower and each of its Subsidiaries has obtained all consents, approvals and authorizations of, made all declarations or filings with, and given all notices to, all Governmental Authorities that are necessary to continue their respective businesses as currently conducted.

None of Borrower, any of its Subsidiaries, or any of Borrower's or its Subsidiaries' Affiliates or any of their respective agents acting or benefiting in any capacity in connection with the transactions contemplated by this Agreement is (i) in violation of any Anti-Terrorism Law, (ii) engaging in or conspiring to engage in any transaction that evades or avoids, or has the purpose of evading or avoiding or attempts to violate, any of the prohibitions set forth in any Anti-Terrorism Law, or (iii) is a Blocked Person. None of Borrower, any of its Subsidiaries, or to the knowledge of Borrower and any of their Affiliates or agents, acting or benefiting in any capacity in connection with the transactions contemplated by this Agreement, (x) conducts any business or engages in making or receiving any contribution of funds, goods or services to or for the benefit of any Blocked Person, or (y) deals in, or otherwise engages in any transaction relating to, any property or interest in property blocked pursuant to Executive Order No. 13224, any similar executive order or other Anti-Terrorism Law. None of the funds to be provided under this Agreement will be used, directly or indirectly, (a) for any activities in violation of any applicable anti-money laundering, economic sanctions and anti-bribery laws and regulations laws and regulations or (b) for any payment to any governmental official or employee, political party, official of a political party, candidate for political office, or anyone else acting in an official capacity, in order to obtain, retain or direct business or obtain any improper advantage, in violation of the United States Foreign Corrupt Practices Act of 1977, as amended.

Information Correct and Current. No information, report, Advance Request, financial statement, exhibit or schedule furnished, by or on behalf of Borrower to Lender in connection with any Loan Document or included therein or delivered pursuant thereto contained, contains or will contain any material misstatement of fact or omitted, omits or will omit to state any material fact necessary to make the statements therein, in the light of the circumstances under which they were, are or will be made, not misleading at the time such statement was made or deemed made. Additionally, any and all financial or business projections provided by Borrower to Lender shall be (i) provided in good faith and based on the most current data and information available to

Borrower, (ii) the most current of such projections provided to the Board, and (iii) are based on reasonable assumptions not viewed as facts and that actual results during the period or periods covered by such projections and forecast may differ from the projected or forecasted results.

Tax Matters. Except as described on Schedule 5.8, (a) Borrower has filed all federal, state and local tax returns that it is required to file, (b) Borrower has duly paid or fully reserved for all taxes or installments thereof (including any interest or penalties) as and when due, which have or may become due pursuant to such returns, and (c) Borrower has paid or fully reserved for any tax assessment received by Borrower for the three (3) years preceding the Restatement Date, if any (including any taxes being contested in good faith and by appropriate proceedings).

Intellectual Property Claims. Borrower is the sole owner of, or otherwise has the right to use, the Intellectual Property. Except as described on Schedule 5.9, (i) each of the material Copyrights, Trademarks and Patents is valid and enforceable, (ii) no material part of the Intellectual Property has been judged invalid or unenforceable, in whole or in part, and (iii) no claim has been made in writing to Borrower that any material part of the Intellectual Property violates the rights of any third party. Exhibit D is a true, correct and complete list of each of Borrower's Patents, registered Trademarks, registered Copyrights, and material agreements under which Borrower licenses Intellectual Property from third parties (other than shrink-wrap software licenses and other licenses for over-the-counter software), together with application or registration numbers, as applicable, owned by Borrower or any Subsidiary, in each case as of the Restatement Date. Borrower is not in material breach of, nor has Borrower failed to perform any material obligations under, any of the foregoing contracts, licenses or agreements and, to uniQure Holdings' knowledge, no third party to any such contract, license or agreement is in material breach thereof or has failed to perform any material obligations thereunder.

Intellectual Property. Except as described on Schedule 5.10, Borrower has, or in the case of any proposed business, will have, all material rights with respect to Intellectual Property necessary in the operation or conduct of Borrower's business as currently conducted and proposed to be conducted by Borrower, Without limiting the generality of the foregoing, and in the case of Licenses, except for restrictions that are unenforceable under Division 9 of the UCC, Borrower has the right, to the extent required to operate Borrower's business, to freely transfer, license or assign Intellectual Property without condition, restriction or payment of any kind (other than license payments in the ordinary course of business) to any third party, and Borrower owns or has the right to use, pursuant to valid licenses, all software development tools, library functions, compilers and all other third-party software and other items that are necessary in the design, development, promotion, sale, license, manufacture, import, export, use or distribution of Borrower Products.

Borrower Products. Except as described on Schedule 5.11, no Intellectual Property owned by Borrower or Borrower Product has been or is subject to any actual or, to the knowledge of Borrower, threatened litigation, proceeding or outstanding decree, order, judgment, settlement agreement or stipulation that restricts in any material manner Borrower's use, transfer or licensing thereof or that may materially affect the validity, use or enforceability thereof. There is no decree, order, judgment, agreement, stipulation, arbitral award or other provision entered into in connection with any litigation or proceeding that obligates Borrower to grant licenses or ownership interest in any future Intellectual Property related to the operation or

conduct of the business of Borrower or Borrower Products. Borrower has not received any written notice or claim, or, to the knowledge of Borrower, oral notice or claim, challenging or questioning Borrower's ownership in any Intellectual Property (or written notice of any claim challenging or questioning the ownership in any licensed Intellectual Property of the owner thereof) or suggesting that any third party has any claim of legal or beneficial ownership with respect thereto nor, to Borrower's knowledge, is there a reasonable basis for any such claim. To Borrower's knowledge, neither Borrower's use of its Intellectual Property nor the production and sale of Borrower Products infringes the Intellectual Property or other rights of others.

Financial Accounts. Exhibit E, as may be updated by the Borrower in a written notice provided to Lender after the Restatement Date, is a true, correct and complete list of (a) all banks and other financial institutions at which Borrower or any Subsidiary maintains Deposit Accounts and (b) all institutions at which Borrower or any Subsidiary maintains an account holding Investment Property, and such exhibit correctly identifies the name, address and telephone number of each bank or other institution, the name in which the account is held, a description of the purpose of the account, and the complete account number therefor.

Employee Loans. Borrower has no outstanding loans to any employee, officer or director of the Borrower nor has Borrower guaranteed the payment of any loan made to an employee, officer or director of the Borrower by a third party.

Capitalization and Subsidiaries. uniQure Holdings' capitalization as of the Restatement Date is set forth on Schedule 5.14 annexed hereto. uniQure Holdings does not own any stock, partnership interest or other securities of any Person, except for Permitted Investments. Attached as Schedule 5.14, as may be updated by uniQure Holdings in a written notice provided after the Restatement Date, is a true, correct and complete list of each Subsidiary.

Centre of main interests and establishments. uniQure Bio has its "centre of main interests" (as that term is used in article 3(1) of The Council of the European Union Regulation No. 1346/2000 on Insolvency Proceedings) in the Netherlands.

INSURANCE; INDEMNIFICATION

Coverage. uniQure Holdings shall cause to be carried and maintained (by itself or its Subsidiaries) commercial general liability insurance, on an occurrence form, against risks customarily insured against in uniQure Holdings's line of business. Such risks shall include the risks of bodily injury, including death, property damage, personal injury, advertising injury, and contractual liability per the terms of the indemnification agreement found in Section 6.3. uniQure Holdings or its Subsidiaries must maintain a minimum of $1,000,000 of commercial general liability insurance for each occurrence and $2,000,000 in the aggregate. uniQure Holdings or its Subsidiaries has and agrees to maintain a minimum of $2,000,000 of directors' and officers' insurance for each occurrence and $5,000,000 in the aggregate. So long as there are any Secured Obligations outstanding, uniQure Holdings shall also cause or procure that its Subsidiaries cause to be carried and maintained insurance upon the Collateral, insuring against all risks of physical loss or damage howsoever caused, in an amount not less than the full replacement cost of the Collateral, provided that such insurance may be subject to standard

exceptions and deductibles. uniQure Holdings or its Subsidiaries shall also carry and maintain a fidelity insurance policy in an amount not less than $100,000.

Certificates. uniQure Holdings shall deliver to Lender certificates of insurance that evidence uniQure Holdings or its Subsidiaries compliance with its insurance obligations in Section 6.1 and the obligations contained in this Section 6.2. uniQure Holding's (or its Subsidiaries) insurance certificate shall state Lender is an additional insured for commercial general liability, a loss payee for all risk property damage insurance, subject to the insurer's approval, a loss payee for fidelity insurance, and a loss payee for property insurance and additional insured for liability insurance for any future insurance that uniQure Holdings or its Subsidiaries may acquire from such insurer, unless any right under the liability insurance is restricted from being pledged under Section 7:954(4) of the Dutch Civil Code. Attached to the certificates of insurance will be additional insured endorsements for liability and lender's loss payable endorsements for all risk property damage insurance and fidelity. Unless an Event of Default shall have occurred and be continuing, all insurance proceeds shall be paid or turned over to uniQure Holdings or its Subsidiaries, as applicable. All certificates of insurance will provide for a minimum of thirty (30) days advance written notice to Lender of cancellation or any other change adverse to Lender's interests. Any failure of Lender to scrutinize such insurance certificates for compliance is not a waiver of any of Lender's rights, all of which are reserved. Borrower shall provide Agent with copies of each insurance policy, and upon entering or amending any insurance policy required hereunder, Borrower shall provide Agent with copies of such policies and shall promptly deliver to Agent updated insurance certificates with respect to such policies.

Indemnity. Borrower agrees to indemnify and hold Lender and its officers, directors, employees, agents, in-house attorneys, representatives and shareholders harmless from and against any and all claims, costs, expenses, damages and liabilities (including such claims, costs, expenses, damages and liabilities based on liability in tort:, including strict liability in tort), including reasonable documented attorneys' fees and disbursements and other costs of investigation or defense (including those incurred upon any appeal), that may be instituted or asserted against or incurred by Lender or any such Person as the result of credit having been extended, suspended or terminated under this Agreement and the other Loan Documents or the administration of such credit, or in connection with or arising out of the transactions contemplated hereunder and thereunder, or any actions or failures to act in connection therewith, or arising out of the disposition or utilization of the Collateral, excluding in all cases claims resulting solely from Lender's gross negligence or willful misconduct Borrower agrees to pay, and to save Lender harmless from, any and all liabilities with respect to, or resulting from any delay in paying, any and all excise, sales or other similar taxes (excluding taxes imposed on or measured by the net income of Lender) that may be payable or determined to be payable with respect to any of the Collateral or this Agreement. This Section 6.3 shall survive the repayment of indebtedness under, and otherwise shall survive the expiration or other termination of, the Agreement.

COVENANTS OF BORROWER

Borrower agrees as follows:

Financial Reports. uniQure Holdings shall furnish to Lender the financial statements and reports listed hereinafter (the "**Financial Statements**"):

as soon as practicable (and in any event within 30 days) after the end of each month, its unaudited interim and year-to-date financial statements as of the end of such month (prepared on a consolidated and consolidating basis, if applicable), including balance sheet and related statements of income accompanied by a report detailing any material contingencies (including the commencement of any material litigation by or against the Obligors) or any other occurrence that would reasonably be expected to have a Material Adverse Effect, all certified by uniQure Holdings' Chief Executive Officer, Chief Financial Officer, Chief Accounting Officer or Global Controller to the effect that they have been prepared in accordance with Accounting Standards, except (i) for the absence of footnotes, (ii) that they are subject to normal year-end adjustments, and (iii) they do not contain certain non-cash items that are customarily included in quarterly and annual financial statements;

as soon as practicable (and in any event within 60 days) after the end of each calendar quarter, unaudited interim and year-to-date financial statements as of the end of such calendar quarter (prepared on a consolidated and consolidating basis, if applicable), including balance sheet and related statements of income and cash flows accompanied by a report detailing any material contingencies (including the commencement of any material litigation by or against Borrower) or any other occurrence that would reasonably be expected to have a Material Adverse Effect, certified by uniQure Holdings' Chief Executive Officer, Chief Financial Officer, Chief Accounting Officer or Global Controller to the effect that they have been prepared in accordance with Accounting Standards, except (i) for the absence of footnotes, and (ii) that they are subject to normal year-end adjustments; as well as the most recent capitalization table for the Obligors, including the weighted average exercise price of employee stock options;

as soon as practicable (and in any event within one hundred and eighty (180 days)) after the end of each fiscal year, unqualified audited financial statements as of the end of such year (prepared on a consolidated and consolidating basis, if applicable), including balance sheet and related statements of income and cash flows, and setting forth in comparative form the corresponding figures for the preceding fiscal year, certified by a firm of independent certified public accountants selected by uniQure Holdings and reasonably acceptable to Lender, accompanied by any management report from such accountants;

as soon as practicable (and in any event within 30 days) after the end of each month, a Compliance Certificate in the form of Exhibit F;

promptly after the sending or filing thereof, as the case may be, copies of any proxy statements, financial statements or reports that US Borrower has made available to holders of its capital stock and copies of any regular, periodic and special reports or registration statements that US Borrower files with the Securities and Exchange Commission or any governmental authority that may be substituted therefor, or any national securities exchange;

notify Lender in writing at least two (2) weeks in advance of the time and place of any regularly scheduled meeting of the Board (including without limitation telephone, conference call and video meetings). uniQure Holdings shall give Lender copies of all notices, minutes, consents and other materials uniQure Holdings provides to its directors in connection with said meetings if reasonably requested by Lender;

Borrower at all times shall maintain Cash and/or cash equivalents on deposit in a deposit or security account located in the United States that is subject to an Account Control Agreement of at least the lesser of (i) 65% of the outstanding principal balance of the Advances or (ii) 100% of all of the worldwide Cash and cash equivalents of the Borrower;

as soon as practicable (and in any event within 30 days) of approval by the Board an annual budget for each financial year as well as budgets, operating plans and other financial information with respect to the Obligors reasonably requested by Lender; and

uniQure Holdings shall not make any change in its (a) accounting policies or reporting practices except in accordance with Accounting Standards, or (b) fiscal years or fiscal quarters. The fiscal year of Borrower shall end on December 31.

The filing of any financial statements, reports or registration statements by uniQure Holdings with the U.S. Securities Exchange Commission (or foreign equivalent thereof) through its electronic filing system shall constitute delivery of such materials to Lender for purposes hereof so long as Borrower timely emails a link of such filings to Lender.

The executed Compliance Certificate may be sent via facsimile to Lender at [*]. All Financial Statements required to be delivered pursuant to clauses (a), (b) and (c) shall be sent via e-mail to [*] provided, that if e-mail is not available or sending such Financial Statements via e-mail is not possible, they shall be sent via facsimile to Lender at: [*], attention Chief Credit Officer.

Management Rights. Borrower shall permit any representative that Lender authorizes, including its attorneys and accountants, to inspect the Collateral and examine and make copies and abstracts of the books of account and records of Borrower at reasonable times and upon reasonable notice during normal business hours. In addition, any such representative shall have the right to meet with management and officers of Borrower to discuss such books of account and records. In addition, Lender shall be entitled at reasonable times and intervals to consult with and advise the management and officers of Borrower concerning significant business issues affecting Borrower. Such consultations shall not unreasonably interfere with Borrower's business operations. The parties intend that the rights granted Lender shall constitute "management rights" within the meaning of 29 C.F.R Section 2510.3-101(d)(3)(ii), but that any advice, recommendations or participation by Lender with respect to any business issues shall not be deemed to give Lender, nor be deemed an exercise by Lender of, control over Borrower's management or policies.

Further Assurances. Borrower shall from time to time execute, deliver and file, alone or with Lender, any financing statements, security agreements, collateral assignments, notices, control agreements, or other documents to perfect or give the highest priority to Lender's Lien on

the Collateral. Borrower shall from time to time procure any instruments or documents as may reasonably be requested by Lender, and take all further action that may be necessary or desirable, or that Lender may reasonably request, to perfect and protect the Liens granted hereby and thereby. In addition, and for such purposes only, Borrower hereby authorizes Lender to execute and deliver on behalf of Borrower and to file such financing statements, collateral assignments, notices, control agreements, security agreements and other documents necessary to grant, perfect and give the highest priority to Lender's Lien on the Collateral without the signature of Borrower either in Lender's name or in the name of Lender as agent and attorney-in-fact for Borrower. Borrower shall protect and defend Borrower's title to the Collateral and Lender's Lien thereon against all Persons claiming any interest adverse to Borrower or Lender other than Permitted Liens.

Indebtedness. Borrower shall not create, incur, assume, guarantee or be or remain liable with respect to any Indebtedness, or permit any Subsidiary so to do, other than Permitted Indebtedness, or prepay any Indebtedness or take any actions which impose on Borrower an obligation to prepay any Indebtedness, except for the conversion of Indebtedness into equity securities and the payment of cash in lieu of fractional shares in connection with such conversion. Borrower shall not make any payments under the Leasehold Financing if an Event of Default has occurred and is continuing.

Collateral. Borrower shall at all times keep the Collateral, the Intellectual Property and all other property and assets used in Borrower's business or in which Borrower now or hereafter holds any interest free and clear from any legal process or Liens whatsoever (except for Permitted Liens), and shall give Lender prompt written notice of any legal process affecting the Collateral, the Intellectual Property, such other property and assets, or any Liens thereon. Borrower shall cause its Subsidiaries to protect and defend such Subsidiary's title to its assets from and against all Persons claiming any interest adverse to such Subsidiary, and Borrower shall cause its Subsidiaries at all times to keep such Subsidiary's property and assets free and clear from any legal process or Liens whatsoever (except for Permitted Liens), and shall give Lender prompt written notice of any legal process affecting such Subsidiary's assets. Borrower shall not agree with any Person other than Lender not to encumber its property.

Investments. Borrower shall not directly or indirectly acquire or own, or make any Investment in or to any Person, or permit any of its Subsidiaries so to do, other than Permitted Investments.

Distributions. Borrower shall not, and shall not allow any Subsidiary to, (a) repurchase or redeem any class of stock or other equity interest other than (i) pursuant to employee, director or consultant repurchase plans, stock option plans or agreements, restricted stock agreements or other similar agreements, provided, however, in each case the repurchase or redemption price does not exceed the original consideration paid for such stock or equity interest or (ii) the delivery of its Ordinary Shares upon conversion of Permitted Convertible Debt; (b) declare or pay any cash dividend or make a cash distribution on any class of stock or other equity interest, except that (i) a Subsidiary may pay dividends or make distributions to Borrower and (ii) Borrower may make cash payments in lieu of issuing fractional shares in connection with a conversion of Permitted Convertible Debt into Ordinary Shares; (c) lend money to any employees, officers or directors or guarantee the payment of any such loans granted by a third

party in excess of $250,000 in the aggregate; or (d) waive, release or forgive any indebtedness owed by any employees, officers or directors in excess of $250,000 in the aggregate.

Transfers. Except for Permitted Transfers, Borrower shall not voluntarily or involuntarily transfer, sell, lease, license, lend or in any other manner convey any equitable, beneficial or legal interest in any material portion of their assets.

Mergers or Acquisitions. uniQure Holdings shall not merge or consolidate, or permit any of its Subsidiaries to merge or consolidate, with or into any other business organization (other than mergers or consolidations of (i) a Subsidiary into an Obligor, or (ii) of a Subsidiary which is not an Obligor into any Subsidiary or into an Obligor, provided, in each case, that with respect to any merger into an Obligor, Obligor is the surviving entity) or acquire, or permit any of its Subsidiaries to acquire, all or substantially all of the capital stock or property of another Person.

Taxes. Borrower and its Subsidiaries shall pay when due all taxes, fees or other charges of any nature whatsoever (together with any related interest or penalties) now or hereafter imposed or assessed against Borrower, Lender or the Collateral or upon Borrower's ownership, possession, use, operation or disposition thereof or upon Borrower's rents, receipts or earnings arising therefrom. Borrower shall file on or before the due date therefor all personal property tax returns in respect of the Collateral. Notwithstanding the foregoing, Borrower may contest, in good faith and by appropriate proceedings, taxes for which Borrower maintains adequate reserves therefor in accordance with Accounting Standards.

Corporate Changes. Neither Borrower nor any Subsidiary shall change its corporate name, legal form or jurisdiction of formation without twenty (20) days' prior written notice to Lender. Neither Borrower nor any Subsidiary shall relocate its principal place of business unless it has provided prior written notice to Lender and such relocation is within the Netherlands or the United States or within the same country as its previous location. Neither Borrower nor any Subsidiary shall relocate any item of Collateral (other than (x) sales of movable assets in the ordinary course of business, (y) relocations of movable assets having an aggregate value of up to $250,000 in any fiscal year, and (z) relocations of Collateral from a location described on Exhibit C to another location described on Exhibit C) unless (i) it has provided prompt written notice to Lender, (ii) such relocation is within the Netherlands or the United States or within the same country as its previous location, and (iii) if such relocation is to a third party bailee in the United States, it has used commercially reasonable efforts to deliver a bailee agreement in form and substance reasonably acceptable to Lender.

Deposit Accounts. No Obligor shall maintain any Deposit Accounts (other than (i) accounts consisting of the proceeds from the Leasehold Financing so long as the aggregate amount in such accounts do not exceed $10,000,000 and (ii) payroll, trust or escrow accounts), or accounts holding Investment Property, except with respect to which Lender has an Account Control Agreement and/or a right of pledge (subject only to a Lien under clause (xii) of the definition of Permitted Liens); provided however, Obligor shall (a) obtain Account Control Agreements for its respective accounts at Rabobank National Association and (b) deliver a completed and executed Perfection Certificate, in each case, no later than 30 Business Days after the Restatement Date.

Subsidiaries. Borrower shall notify Lender of each Subsidiary formed subsequent to the Restatement Date and, within 15 days of formation, shall cause any such Subsidiary to execute and deliver to Lender a Joinder Agreement.

Pensions. Borrower shall ensure that all pension schemes operated by or maintained for the benefit of members of the Borrower and/or any of their employees are funded to the extent required by applicable law and regulations where failure to do so would be reasonably likely to have a Material Adverse Effect.

Non-Obligors. The revenue of Subsidiaries which are not Obligors shall not exceed €250,000 in the aggregate on an annual basis. The fair market value of the assets of Subsidiaries which are not Obligors shall not exceed €500,000 in the aggregate at any given time.

Use of Proceeds. Borrower agrees that the proceeds of the Loans shall be used solely to pay related fees and expenses in connection with this Agreement and for working capital and general corporate purposes. The proceeds of the Loans will not be used in violation of applicable Anti-Corruption Laws or applicable Sanctions.

Compliance with Laws.

Borrower shall maintain, and shall cause its Subsidiaries to maintain, compliance in all material respect with all applicable laws, rules or regulations (including any law, rule or regulation with respect to the making or brokering of loans or financial accommodations), and shall, or cause its Subsidiaries to, obtain and maintain all required governmental authorizations, approvals, licenses, franchises, permits or registrations reasonably necessary in connection with the conduct of Borrower's business.

Neither Borrower nor any of its Subsidiaries shall, nor shall Borrower or any of its Subsidiaries permit any Affiliate to, directly or indirectly, knowingly enter into any documents, instruments, agreements or contracts with any Person listed on the OFAC Lists. Neither Borrower nor any of its Subsidiaries shall, nor shall Borrower or any of its Subsidiaries, permit any Affiliate to, directly or indirectly, (i) conduct any business or engage in any transaction or dealing with any Blocked Person, including, without limitation, the making or receiving of any contribution of funds, goods or services to or for the benefit of any Blocked Person, (ii) deal in, or otherwise engage in any transaction relating to, any property or interests in property blocked pursuant to Executive Order No. 13224 or any similar executive order or other Anti-Terrorism Law, or (iii) engage in or conspire to engage in any transaction that evades or avoids, or has the purpose of evading or avoiding, or attempts to violate, any of the prohibitions set forth in Executive Order No. 13224 or other Anti-Terrorism Law.

Borrower has implemented and maintains in effect policies and procedures designed to ensure compliance by the Borrower, its Subsidiaries and their respective directors, officers, employees and agents with applicable Anti-Corruption Laws and applicable Sanctions, and Borrower, its Subsidiaries and their respective officers and employees and to the knowledge of Borrower its directors and agents, are in compliance with applicable Anti-Corruption Laws and applicable Sanctions in all material respects.

None of Borrower, any of its Subsidiaries or any of their respective directors, officers or employees, or to the knowledge of Borrower, any agent for Borrower or its Subsidiaries that will act in any capacity in connection with or benefit from the credit facility established hereby, is a Sanctioned Person. No Loan, use of proceeds or other transaction contemplated by this Agreement will violate applicable Anti-Corruption Laws or applicable Sanctions.

Transactions with Affiliates. Borrower shall not and shall not permit any Subsidiary to, directly or indirectly, enter into or permit to exist any transaction of any kind with any Affiliate of Borrower or such Subsidiary on terms that are less favorable to Borrower or such Subsidiary, as the case may be, than those that might be obtained in an arm's length transaction from a Person who is not an Affiliate of Borrower or such Subsidiary; provided that no such restriction shall apply where the value of any transaction with any Affiliate of Borrower is less than Five Hundred Thousand Dollars ($500,000).

Right to Invest. Borrower agrees that, prior to the repayment in full of all 2021 Term Loan Advances, Lender, any of its affiliates and/or (subject to Borrower's consent, which consent shall not be unreasonably withheld, conditioned or delayed) any other assignees or nominees, shall have the right, in their discretion, to invest up to an aggregate amount of $2,000,000 in any Subsequent Financing on the same terms, conditions and pricing afforded to others participating in any such Subsequent Financing, provided, however, that such aggregate amount for any such Subsequent Financing may be reduced to an amount determined in good faith by the managing underwriter of any such Subsequent Financing if such managing underwriter determines, in its reasonable discretion, that such reduction is required as a result of bona fide marketing factors. Borrower shall notify Lender within twenty-four (24) hours of the public announcement of any such Subsequent Financing and Lender shall notify Borrower of its intention to participate in such Subsequent Financing as soon as possible thereafter, but in any event, not later than eight (8) hours prior to the pricing of such Subsequent Financing.

EVENTS OF DEFAULT

The occurrence of any one or more of the following events shall be an Event of Default:

Payments. Borrower fails to pay any amount when due under this Agreement or any of the other Loan Documents unless its failure to pay is caused by administrative or technical error and payment is made within three Business Days of its due date; or

Covenants. Borrower breaches or defaults in the performance of any covenant or Secured Obligation under this Agreement, or any of the other Loan Documents (other than a breach or default covered by Section 8.1), and (a) with respect to a default under any covenant under this Agreement (other than under Sections 6, 7.1(g), 7.5, 7.6, 7.7, 7.8, 7.9, 7.15, 7.16, 7.17 or 7.19) such default continues for more than 15 Business Days after the earlier of the date on which (i) Agent or Lender has given notice of such default to Borrower and (ii) Borrower has actual knowledge of such default or (b) with respect to a default under any of Sections 6, 7.1(g), 7.5, 7.6, 7.7, 7.8, 7.9, 7.15, 7.16, 7.17 or 7.19, the occurrence of such default; or

Material Adverse Effect. A circumstance (other than the Extera Judgment) has occurred that would reasonably be expected to have a Material Adverse Effect; or

Other Loan Documents. The occurrence of any default under any Loan Document and such default continues for more than 15 Business Days after the earlier of (a) Lender has given notice of such default to Borrower, or (b) Borrower has actual knowledge of such default; or

Representations. Any material representation or warranty made by Borrower in any Loan Document shall have been false or misleading in any material respect; or

Insolvency. Borrower (A) (i) shall make an assignment for the benefit of creditors; or (ii) shall be unable to pay its debts as they become due, or be unable to pay or perform under the Loan Documents, or shall become insolvent; or (iii) shall file a voluntary petition in bankruptcy; or (iv) shall file any petition, answer, or document seeking for itself any reorganization, arrangement, composition, readjustment, liquidation, dissolution or similar relief under any present or future statute, law or regulation pertinent to such circumstances; or (v) shall seek or consent to or acquiesce in the appointment of any trustee, receiver, or liquidator of Borrower or of all or any substantial part (i.e., 33-1/3% or more) of the assets or property of Borrower; or (vi) shall cease operations of its business as its business has normally been conducted, or terminate substantially all of its employees; (vii) Borrower or its directors or majority shareholders shall take any action initiating any of the foregoing actions described in clauses (i) through (vi); or (B) either (i) forty-five (45) days shall have expired after the commencement of an involuntary action against Borrower seeking reorganization, arrangement, composition, readjustment, liquidation, dissolution or similar relief under any present or future statute, law or regulation, without such action being dismissed or all orders or proceedings thereunder affecting the operations or the business of Borrower being stayed; or (ii) a stay of any such order or proceedings shall thereafter be set aside and the action setting it aside shall not be timely appealed; or (iii) Borrower shall file any answer admitting or not contesting the material allegations of a petition filed against Borrower in any such proceedings; or (iv) the court in which such proceedings are pending shall enter a decree or order granting the relief sought in any such proceedings; or (v) thirty (30) days shall have expired after the appointment, without the consent or acquiescence of Borrower, of any trustee, receiver or liquidator of Borrower or of all or any substantial part of the properties of Borrower without such appointment being vacated; or

Attachments; Judgments. Any portion of Borrower's assets is attached or seized, or a levy is filed against any such assets (and such attachment, seizure or levy is not lifted or released within 30 days), or a judgment or judgments (no longer subject to appeal) (excluding the Extera Judgment) is/are entered for the payment of money, individually or in the aggregate, of at least $2,000,000, unless otherwise waived by Lender in its reasonable discretion, or Borrower is enjoined or in any way prevented by court order from conducting any part of its business; or

Other Obligations. The occurrence of any default (beyond any applicable grace, appeal or cure periods) under any agreement or obligation of Borrower involving any Indebtedness in excess of $1,000,000, or the occurrence of any default by the Borrower under any agreement or obligation of Borrower that could reasonably be expected to have a Material Adverse Effect.

REMEDIES

General. On and at any time after the occurrence of an Event of Default which is continuing (i) Lender may, at its option, accelerate and demand payment of all or any part of the

Secured Obligations and the 2018 Prepayment Charge and declare them to be immediately due and payable (provided, that upon the occurrence of an Event of Default of the type described in Section 8.6, all of the Secured Obligations shall automatically be accelerated and made due and payable, in each case without any further notice or act), and (ii) Lender may notify any of Borrower's account debtors to make payment directly to Lender, compromise the amount of any such account on Borrower's behalf and endorse Lender's name without recourse on any such payment for deposit directly to Lender's account.

Collection; Foreclosure. Unless otherwise agreed in the Collateral Documents, on and at any time after the occurrence of an Events of Default which is continuing, Lender may, at any time or from time to time, apply, collect, liquidate, sell in one or more sales, lease or otherwise dispose of, any or all of the Collateral, in its then condition or following any commercially reasonable preparation or processing, in such order as Lender may elect, in each case to the extent permitted under applicable law. Any such sale may be made either at public or private sale at its place of business or elsewhere. Borrower agrees that any such public or private sale may occur upon ten (10) calendar days' prior written notice to Borrower. Lender may require Borrower to assemble the Collateral and make it available to Lender at a place designated by Lender that is reasonably convenient to Lender and Borrower. The proceeds of any sale, disposition or other realization upon all or any part of the Collateral shall be applied by Lender in the following order of priorities:

> First, to Lender in an amount sufficient to pay in full Lender's costs and professionals' and advisors' fees and expenses as described in Section 11.11;
>
> Second, to Lender in an amount equal to the then unpaid amount of the Secured Obligations (including principal, interest, and the Default Rate interest), in such order and priority as Lender may choose in its sole discretion; and
>
> Finally, after the full, final, and indefeasible payment in Cash of all of the Secured Obligations, to any creditor holding a junior Lien on the Collateral, or to Borrower or its representatives or as a court of competent jurisdiction may direct.

Lender shall be deemed to have acted reasonably in the custody, preservation and disposition of any of the Collateral if it complies with the obligations of a secured party under the UCC.

No Waiver. Lender shall be under no obligation to marshal any of the Collateral for the benefit of Borrower or any other Person, and Borrower expressly waives all rights, if any, to require Lender to marshal any Collateral.

Cumulative Remedies. The rights, powers and remedies of Lender hereunder shall be in addition to all rights, powers and remedies given by statute or rule of law and are cumulative. The exercise of any one or more of the rights, powers and remedies provided herein shall not be construed as a waiver of or election of remedies with respect to any other rights, powers and remedies of Lender.

MISCELLANEOUS

Severability. Whenever possible, each provision of this Agreement shall be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement shall be prohibited by or invalid under such law, such provision shall be ineffective only to the extent and duration of such prohibition or invalidity, without invalidating the remainder of such provision or the remaining provisions of this Agreement.

Notice. Except as otherwise provided herein, any notice, demand, request, consent, approval, declaration, service of process or other communication (including the delivery of Financial Statements) that is required, contemplated, or permitted under the Loan Documents or with respect to the subject matter hereof shall be in writing, and shall be deemed to have been validly served, given, delivered, and received upon the earlier of: (i) the day of transmission by facsimile or hand delivery or delivery by an overnight express service or overnight mail delivery service; or (ii) the third calendar day after deposit in the United States mails, with proper first class postage prepaid, in each case addressed to the party to be notified as follows:

[*]

or to such other address as each party may designate for itself by like notice.

Entire Agreement; Amendments. This Agreement and the other Loan Documents constitute the entire agreement and understanding of the parties hereto in respect of the subject matter hereof and thereof, and supersede and replace in their entirety any prior proposals, term sheets, non-disclosure or confidentiality agreements, letters, negotiations or other documents or agreements, whether written or oral, with respect to the subject matter hereof or thereof (including Lender's proposal letter dated November 8, 2018). None of the terms of this Agreement or any of the other Loan Documents may be amended except by an instrument executed by each of the parties hereto.

No Strict Construction. The parties hereto have participated jointly in the negotiation and drafting of this Agreement. In the event an ambiguity or question of intent or interpretation arises, this Agreement shall be construed as if drafted jointly by the parties hereto and no presumption or burden of proof shall arise favoring or disfavoring any party by virtue of the authorship of any provisions of this Agreement.

No Waiver. The powers conferred upon Lender by this Agreement are solely to protect its rights hereunder and under the other Loan Documents and its interest in the Collateral and shall not impose any duty upon Lender to exercise any such powers. No omission or delay by Lender at any time to enforce any right or remedy reserved to it, or to require performance of any of the terms, covenants or provisions hereof by Borrower at any time designated, shall be a waiver of any such right or remedy to which Lender is entitled, nor shall it in any way affect the right of Lender to enforce such provisions thereafter.

Survival. All agreements, representations and warranties contained in this Agreement and the other Loan Documents or in any document delivered pursuant hereto or thereto shall be

for the benefit of Lender and shall survive the execution and delivery of this Agreement and the expiration or other termination of this Agreement.

Successors and Assigns. The provisions of this Agreement and the other Loan Documents shall inure to the benefit of and be binding on Borrower and its permitted assigns (if any). Borrower shall not assign its obligations under this Agreement or any of the other Loan Documents without Lender's express prior written consent, and any such attempted assignment shall be void and of no effect. Lender may assign, transfer, or endorse its rights hereunder and under the other Loan Documents without prior notice to Borrower, and all of such rights shall inure to the benefit of Lender's successors and assigns.

Governing Law. This Agreement and the other Loan Documents shall be governed by, and construed and enforced in accordance with, the laws of the Netherlands.

Jurisdiction. The courts (*Rechtbank*) of Amsterdam, the Netherlands, subject to ordinary appeal and final appeal shall have exclusive jurisdiction to hear and determine any suit, action or proceeding and to settle any disputes arising out of or in connection with this Agreement and the other Loan Documents (including a dispute regarding the existence, validity or termination of this Agreement or the consequences of its nullity) and, for such purposes, each of the parties hereto irrevocably submits to the exclusive jurisdiction of such courts. This Section is for the benefit of the Lender only. As a result, the Lender may take proceedings relating to a dispute in any other courts with jurisdiction. To the extent allowed by law, the Lender may take concurrent proceedings in any number of jurisdictions.

Professional Fees. Borrower promises to pay Lender's documented out-of-pocket fees and expenses necessary to finalize the loan documentation, including but not limited to reasonable documented attorneys' fees, UCC searches, filing costs, and other miscellaneous expenses up to a maximum amount of $10,000 and Agent confirms as of the Restatement Date that there are no other legal fees owing as of such date. In addition, Borrower promises to pay any and all reasonable documented attorneys' and other professionals' fees and expenses (including fees and expenses of in-house counsel) incurred by Lender after the Restatement Date in connection with or related to: (a) the Loan; (b) the administration, collection, or enforcement of the Loan; (c) the amendment or modification of the Loan Documents; (d) any waiver, consent, release, or termination under the Loan Documents; (e) the protection, preservation, sale, lease, liquidation, or disposition of Collateral or the exercise of remedies with respect to the Collateral; (f) any legal, litigation, administrative, arbitration, or out of court proceeding in connection with or related to Borrower or the Collateral, and any appeal or review thereof; and (g) any bankruptcy, restructuring, reorganization, assignment for the benefit of creditors, workout, foreclosure, or other action related to Borrower, the Collateral, the Loan Documents, including representing Lender in any adversary proceeding or contested matter commenced or continued by or on behalf of Borrower's estate, and any appeal or review thereof.

Confidentiality. Lender acknowledges that all financial statements provided to Lender by Borrower and certain items of Collateral and information provided to Lender by Borrower are confidential and proprietary information of Borrower, if and to the extent such information either (x) is marked as confidential by Borrower at the time of disclosure, or (y) should reasonably be understood to be confidential (the "**Confidential Information**"). Accordingly, Lender agrees

that any Confidential Information it may obtain in the course of acquiring, administering, or perfecting Lender's security interest in the Collateral shall not be disclosed to any other person or entity in any manner whatsoever, in whole or in part, without the prior written consent of Borrower, except that Lender may disclose any such information: (a) to its own directors, officers, employees, accountants, counsel and other professional advisors and to its affiliates if Lender in its sole discretion determines that any such party should have access to such information in connection with such party's responsibilities in connection with the Loan or this Agreement and, provided that such recipient of such Confidential Information either (i) agrees to be bound by the confidentiality provisions of this paragraph or (ii) is otherwise subject to confidentiality restrictions that reasonably protect against the disclosure of Confidential Information; (b) if such information is generally available to the public; (c) if required or appropriate in any report, statement or testimony submitted to any governmental authority having or claiming to have jurisdiction over Lender; (d) if required or appropriate in response to any summons or subpoena or in connection with any litigation, to the extent permitted or deemed advisable by Lender's counsel; (e) to comply with any legal requirement or law applicable to Lender; (f) to the extent reasonably necessary in connection with the exercise of any right or remedy under any Loan Document, including Lender's sale, lease, or other disposition of Collateral after the occurrence and during the continuance of an Event of Default; (g) to any participant or assignee of Lender or any prospective participant or assignee; provided, that such participant or assignee or prospective participant or assignee agrees in writing to be bound by this Section prior to disclosure; or (h) otherwise with the prior consent of Borrower; provided, that any disclosure made in violation of this Agreement shall not affect the obligations of Borrower or any of its affiliates or any guarantor under this Agreement or the other Loan Documents.

Assignment of Rights. Borrower acknowledges and understands that Lender may sell and assign all or part of its interest hereunder and under the Loan Documents to any person or entity (an "**Assignee**"). After such assignment the term "Lender" as used in the Loan Documents shall mean and include such Assignee, and such Assignee shall be vested with all rights, powers and remedies of Lender hereunder with respect to the interest so assigned; but with respect to any such interest not so transferred, Lender shall retain all rights, powers and remedies hereby given. No such assignment by Lender shall relieve Borrower of any of its obligations hereunder. Lender agrees that in the event of any transfer by it of the Note(s) (if any), it will endorse thereon a notation as to the portion of the principal of the Note(s), which shall have been paid at the time of such transfer and as to the date to which interest shall have been last paid thereon.

Revival of Secured Obligations. This Agreement and the Loan Documents shall remain in full force and effect and continue to be effective if any petition is filed by or against Borrower for liquidation or reorganization, if Borrower becomes insolvent or makes an assignment for the benefit of creditors, if a receiver or trustee is appointed for all or any significant part of Borrower's assets, or if any payment or transfer of Collateral is recovered from Lender. The Loan Documents and the Secured Obligations and Collateral security shall continue to be effective, or shall be revived or reinstated, as the case may be, if at any time payment and performance of the Secured Obligations or any transfer of Collateral to Lender, or any part thereof is rescinded, avoided or avoidable, reduced in amount, or must otherwise be restored or returned by, or is recovered from, Lender or by any obligee of the Secured Obligations, whether as a "voidable preference," "fraudulent conveyance," or otherwise, all as though such payment,

performance, or transfer of Collateral had not been made. In the event that any payment, or any part thereof, is rescinded, reduced, avoided, avoidable, restored, returned, or recovered, the Loan Documents and the Secured Obligations shall be deemed, without any further action or documentation, to have been revived and reinstated except to the extent of the full, final, and indefeasible payment to Lender in Cash.

Counterparts. This Agreement and any amendments, waivers, consents or supplements hereto may be executed in any number of counterparts, and by different parties hereto in separate counterparts, each of which when so delivered shall be deemed an original, but all of which counterparts shall constitute but one and the same instrument.

Publicity.

Borrower consents to the publication and use by Lender and any of its member businesses and affiliates of (i) Borrower's name (including a brief description of the relationship between Borrower and Lender) and logo for use on Lender's website and as required for the purposes of filings with or reports to governmental authorities required by law, and (ii) after review and approval by Borrower (a) Borrower's name and a hyperlink to Borrower's web site, separately or together, in written and oral presentations, advertising, promotional and marketing materials, client lists, public relations materials or on its web site (together, the "**Lender Publicity Materials**"); (b) the names of officers of Borrower in the Lender Publicity Materials; and (c) Borrower's name, trademarks or servicemarks in any news release concerning Lender.

Neither Borrower nor any of its member businesses and affiliates shall, without Lender's consent, publicize or use, for any purpose other than filings with or reports to governmental authorities required by law and the rules of any applicable securities commission or securities exchange, (i) Lender's name (including a brief description of the relationship between Borrower and Lender), logo or hyperlink to Lender's web site, separately or together, in written and oral presentations, advertising, promotional and marketing materials, client lists, public relations materials or on its web site (together, the "**Borrower Publicity Materials**"); (ii) the names of officers of Lender in the Borrower Publicity Materials; and (iii) Lender's name, trademarks, servicemarks in any news release concerning Borrower.

Existing Loan and Security Agreement Amended and Restated. Upon satisfaction of the conditions precedent to the effectiveness of this Agreement, (a) this Agreement shall amend and restate the Existing Loan and Security Agreement in its entirety (except to the extent that definitions from the Existing Loan and Security Agreement are incorporated herein by reference) and (b) the rights and obligations of the parties under the Existing Loan and Security Agreement shall be subsumed within, and be governed by, this Agreement; provided, however, that the Borrower hereby agrees that all Secured Obligations of the Borrower under, and as defined in, the Existing Loan and Security Agreement and the other Loan Documents shall remain outstanding, shall constitute continuing Secured Obligations secured by the Collateral, and this Agreement shall not be deemed to evidence or result in a novation or repayment and re-borrowing of such obligations and other liabilities. Borrower hereby acknowledges and reaffirms each and every Loan Document entered into in connection with the Existing Loan and Security Agreement and acknowledges that each such Loan Document remains in full force and effect and enforceable against Borrower in accordance with its respective terms after giving

effect to the execution and delivery of this Agreement without further action by Lender, Borrower or any other Person. All reference to the "Loan and Security Agreement" in each such Loan Document shall be deemed to be a reference to this Agreement.

Agency. Lender hereby irrevocably appoints HERCULES CAPITAL, INC. to act on its behalf as agent hereunder and under the other Loan Documents and authorizes the agent to take such actions on its behalf and to exercise such powers as are delegated to the agent by the terms hereof or thereof, together with such actions and powers as are reasonably incidental thereto.

(SIGNATURES TO FOLLOW)

LENDER:

HERCULES CAPITAL, INC.

Signature: _____

Print Name: _____

Title: _____

IN WITNESS WHEREOF, the Obligors and Lender have duly executed and delivered this Loan and Security Agreement as of the day and year first above written.

BORROWER:

UNIQURE BIOPHARMA B.V.
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE, INC.

Signature: _____
Print Name: Matt Kapusta
Title: President and Secretary

OBLIGORS:

UNIQURE N.V. (formerly uniQure B.V.)

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE RESEARCH B.V.
by: uniQure Biopharma RV.,
the Company's Managing Director
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE ASSAY DEVELOPMENT
by: uniQure Biopharma B.V.,
the Company's Managing Director
by: uniQure N.V., its Managing Director

Signature:_____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE QA B.V.
by: uniQure Biopharma B.V.,
the Company's Managing Director
by: uniQure N.V., its Managing Director
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE PROCESS DEVELOPMENT B.V.
by: uniQure .Biopharma B.V.,
the Company's Managing Director
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE, NON CLINICAL B.V.
by: uniQure Biopharma B.V.,
the Company's Managing Director
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE CLINICAL B.V.
by: uniQure Biopharma B.V.,
the Company's Managing Director
Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE IP B.V.
by uniQure N.V. ,
the Company's Managing Director
Signature: _____

Print Name: Matt Kapusta
Title: Managing Director

IN WITNESS WHEREOF, the Obligors and Lender have duly executed and delivered this Loan and Security Agreement as of the day and year first above written.

UNIQURE GmbH

Signature: _____
Print Name: Christian Klemt
Title: Managing Director

Table of Addenda, Exhibits and Schedules

EXHIBIT A
ADVANCE REQUEST

To: Lender: Date _____, 20__

HERCULES CAPITAL, INC.
400 Hamilton Avenue, Suite 310
Palo Alto, CA 94301
Facsimile: [*]
Email: [*]
Attn: Chief Legal Officer and [*]

UNIQURE BIOPHARMA B.V., and UNIQURE, INC., (hereinafter collectively referred to as "**Borrower**") hereby requests from HERCULES CAPITAL, INC. ("**Lender**") a 2021 Term Loan Advance in the amount of _____Dollars ($_____) on _____ (the "**Advance Date**") pursuant to the Second Amended and Restated Loan and Security Agreement between, among others, Borrower and Lender (the "**Agreement**"). Capitalized words and other terms used but not otherwise defined herein are used with the same meanings as defined in the Agreement.

SECTION 1. Please:

(a) Issue a check payable to Borrower _____

or

(h) Wire Funds to Borrower's account _____

Bank: _____
Address: _____
ABA Number: _____
Account Number: _____
Account Name: _____

Borrower represents that the conditions precedent to the Advance set forth in the Agreement are satisfied and shall be satisfied upon the making of such Advance, including but not limited to: (i) that no event that has had or could reasonably be expected to have a Material Adverse Effect has occurred and is continuing; (ii) that the representations and warranties set forth in the Agreement are and shall be true and correct in all material respects on and as of the Advance Date with the same effect as though made on and as of such date, except to the extent such representations and warranties expressly relate to an earlier date; (iii) that Borrower is in compliance with all the terms and provisions set forth in each Loan Document on its part to be observed or performed; and (iv) that as of the Advance Date, no fact or condition exists that would (or would, with the passage of time, the giving of notice, or both) constitute an Event of Default under the Loan Documents. Borrower understands and acknowledges that Lender has the right to review the financial information supporting this representation and, based upon such review in its sole discretion, Lender may decline to fund the requested Advance.

Borrower hereby represents that Borrower's corporate status and principal place of business have not changed since the date of the Agreement or, if the Attachment to this Advance Request is completed, are as set forth in the Attachment to this Advance Request.

Borrower agrees to notify Lender promptly before the funding of the Advance if any of the matters which have been represented above shall not be true and correct on the Advance Date and if Lender has received no such notice before the Advance Date then the statements set forth above shall be deemed to have been made and shall be deemed to be true and correct as of the Advance Date.

Executed as of [_____], 2021

BORROWER:

UNIQURE BIOPHARMA B.V.
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE, INC.

Signature: _____
Print Name: Matt Kapusta
Title: President and Secretary

ATTACHMENT TO ADVANCE REQUEST

Dated: _____

Borrower hereby represents and warrants to Lender that Borrower's current name and organizational status is as follows:

Name: _____

Type of organization: _____

State of organization: _____

Organization file number: _____

Borrower hereby represents and warrants to Lender that the street addresses, cities, states and postal codes of its current locations are as follows:

EXHIBIT B
SECOND AMENDED AND RESTATED PROMISSORY NOTE

SECTION 2. $ _____ Maturity Date _____, 20__

FOR VALUE RECEIVED, (i) UNIQURE BIOPHARMA B.V., a private limited liability company incorporated and existing under the laws of the Netherlands, having its corporate seat at Amsterdam, the Netherlands and registered at the trade register of the Chamber of Commerce for Amsterdam under number 34275365 ("**uniQure Bio**"), (ii) UNIQURE, Inc., a Delaware corporation ("**US Borrower**" and together with uniQure Bio hereinafter collectively referred to as "**Borrower**") hereby promises to pay to the order of [HERCULES CAPITAL FUNDING TRUST 2014-1, a Delaware statutory trust][HERCULES CAPITAL, INC., a Maryland corporation] (the "Lender") or the holder of this Second Amended and Restated Promissory Note (this "**Promissory Note**") at 400 Hamilton Avenue, Suite 310, Palo Alto, CA 94301 or such other place of payment as the holder of this Promissory Note may specify from time to time in writing, in lawful money of the United States of America, the principal amount of _____ Dollars ($_____) or such other principal amount as Lender has advanced to

Borrower, together with interest at a floating rate as set forth in Section [2.1.1(d)][2.1.2(d)] of the Loan Agreement referenced below.

This Promissory Note is the Note referred to in, and is executed and delivered in connection with, that certain Second Amended and Restated Loan and Security Agreement dated May 6, 2016, by and between, among others, Borrower and Lender (as the same may from time to time be amended, modified or supplemented in accordance with its terms, the "**Loan Agreement**"), and is entitled to the benefit and security of the Loan Agreement and the other Loan Documents (as defined in the Loan Agreement), to which reference is made for a statement of all of the terms and conditions thereof. All payments shall be made in accordance with the Loan Agreement. All terms defined in the Loan Agreement shall have the same definitions when used herein, unless otherwise defined herein. An Event of Default under the Loan Agreement shall constitute a default under this Promissory Note.

Borrower agrees to make all payments under this Promissory Note without setoff, recoupment or deduction and regardless of any counterclaim or defense. This Promissory Note has been negotiated and delivered to Lender and is payable in the State of California. This Promissory Note shall be governed by and construed and enforced in accordance with, the laws of the Netherlands, excluding any conflicts of law rules or principles that would cause the application of the laws of any other jurisdiction.

BORROWER:

UNIQURE BIOPHARMA B.V.
by: uniQure N.V., its Managing Director

Signature: _____
Print Name: Matt Kapusta
Title: Managing Director

UNIQURE, INC.

Signature: _____
Print Name: Matt Kapusta
Title: President and Secretary

EXHIBIT C
NAME, LOCATIONS, AND OTHER INFORMATION FOR BORROWER

1. uniQure US represents and warrants to Agent that its current name and organizational status as of the First Amendment Closing Date is as follows:

Name:	UNIQURE, INC.
Type of organization:	Corporation
State of organization:	Delaware
Organization file number:	5330494

2. uniQure represents and warrants to Agent that its current name and organizational status as of the First Amendment Closing Date is as follows:

Name:	UNIQURE BIOPHARMA B.V.
Type of organization:	Private Limited Company
State of organization:	The Netherlands
Organization file number:	34275365

3. Borrower represents and warrants to Agent that for five (5) years prior to the First Amendment Closing Date, Borrower did not do business under any other name or organization or form.

4. Borrower represents and warrants to Agent that its principal executive office is at Paasheuvelweg 25a, 1105 BP Amsterdam, the Netherlands.

EXHIBIT D
BORROWER'S PATENTS, TRADEMARKS, COPYRIGHTS AND LICENSES

[PROVIDED SEPARATELY]

EXHIBIT E
BORROWER'S DEPOSIT ACCOUNTS AND INVESTMENT ACCOUNTS

[*]

EXHIBIT F
COMPLIANCE CERTIFICATE

SECTION 3. Hercules Capital, Inc. (as "Agent")
400 Hamilton Avenue, Suite 310
Palo Alto, CA 94301
SECTION 4. Facsimile: [*]
SECTION 5. Email: [*]
SECTION 6. Attn: [*]

Reference is made to that certain Second Amended and Restated Loan and Security Agreement dated May 6, 2016 and the Loan Documents (as defined therein) entered into in connection with such Second Amended and Restated Loan and Security Agreement all as may be amended from time to time (hereinafter referred to collectively as the "Loan Agreement") by and among Hercules Capital, Inc. (the "Agent"), the several banks and other financial institutions or entities from time to time party thereto (collectively, the "Lender") and Hercules Capital, Inc., as agent for the Lender (the "Agent") and UNIQURE BIOPHARMA B.V. and UNIQURE, Inc., (hereinafter collectively referred to as "Borrower"), as Borrower. All capitalized terms not defined herein shall have the same meaning as defined in the Loan Agreement.

The undersigned is an Officer of UNIQURE N.V., knowledgeable of all UNIQURE N.V.'s financial matters, and is authorized to provide certification of information regarding UNIQURE N.V.; hereby certifies that in accordance with the terms and conditions of the Loan Agreement, UNIQURE N.V. is in compliance for the period ending _____ of all covenants, conditions and terms and hereby reaffirms that all representations and warranties contained therein are true and correct in all material respects on and as of the date of this Compliance Certificate with the same effect as though made on and as of such date, except to the extent such representations and warranties expressly relate to an earlier date, after giving effect in all cases to any standard(s) of materiality contained in the Loan Agreement as to such representations and warranties. Attached are the required documents supporting the above certification. The undersigned further certifies that these are prepared in accordance with Accounting Standards (except for the absence of footnotes with respect to unaudited financial statement and subject to normal year-end adjustments) and are consistent from one period to the next except as explained below.

SECTION 7. REPORTING REQUIREMENT	REQUIRED	CHECK IF ATTACHED
SECTION 8. Interim Financial Statements	Monthly within 30 days	
SECTION 9. Interim Financial Statements	Quarterly within 60 days	
SECTION 10. Audited Financial Statements	FYE within 180 days	

SECTION 11. Total Cash Balance $_____

SECTION 12. US Accounts Balance $_____

Very Truly Yours,

UNIQURE N.V.

Signature: _____

Print Name: _____

Title:

EXHIBIT G
FORM OF JOINDER AGREEMENT

This Joinder Agreement (the "**Joinder Agreement**") is made and dated as of [_____], 20[____], and is entered into by and between _____, a _____ corporation ("**Subsidiary**"), and HERCULES CAPITAL FUNDING TRUST 2014-1, a Delaware statutory trust, as agent on behalf itself and other lenders (collectively, "**Lender**").

RECITALS

A. Subsidiary's Affiliates, (i) UNIQURE BIOPHARMA B.V., and UNIQURE, INC., (hereinafter collectively referred to as "**Borrower**") have, among others, entered into that certain Second Amended and Restated Loan and Security Agreement dated May 6, 2016, with the lenders party thereto, as such agreement may be amended (the "**Loan Agreement**"), together with the other agreements executed and delivered in connection therewith;

B. Subsidiary acknowledges and agrees that it will benefit both directly and indirectly from Borrower's execution of the Loan Agreement and the other agreements executed and delivered in connection therewith;

AGREEMENT

NOW THEREFORE, Subsidiary and Lender agree as follows:

1. The recitals set forth above are incorporated into and made part of this Joinder Agreement. Capitalized terms not defined herein shall have the meaning provided in the Loan Agreement.

2. By signing this Joinder Agreement, Subsidiary shall be bound by the terms and conditions of the Loan Agreement the same as if it were the Borrower (as defined in the Loan Agreement) under the Loan Agreement, mutatis mutandis, provided however, that Lender shall have no duties, responsibilities or obligations to Subsidiary arising under or related to the Loan Agreement or the other agreements executed and delivered in connection therewith. Rather, to the extent that Lender has any duties, responsibilities or obligations arising under or related to the Loan Agreement or the other agreements executed and delivered in connection therewith, those duties, responsibilities or obligations shall flow only to Borrower and not to Subsidiary or any other person or entity. By way of example (and not an exclusive list): (a) Lender's providing notice to Borrower in accordance with the Loan Agreement or as otherwise agreed between Borrower and Lender shall be deemed provided to Subsidiary; (b) a Lender's providing an Advance to Borrower shall be deemed an Advance to Subsidiary; and (c) Subsidiary shall have no right to request an Advance or make any other demand on Lender.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

[SIGNATURE PAGE TO JOINDER AGREEMENT]

SECTION 13. SUBSIDIARY:

By: _____
Name: _____
Title: _____
Address: _____
Telephone: _____
Facsimile: _____

SECTION 14. HERCULES CAPITAL, INC., as agent for Lender

By: _____
Name: _____
Title: _____

Address:
400 Hamilton Ave., Suite 310
Palo Alto, CA 94301
Facsimile: [*]
Telephone: [*]
SECTION 15. [*]

EXHIBIT H
ACH DEBIT AUTHORIZATION AGREEMENT

SECTION 16. Hercules Capital, Inc. (as "Agent")
400 Hamilton Avenue, Suite 310
Palo Alto, CA 94301
SECTION 17. Facsimile: [*]
SECTION 18. Email: [*]
SECTION 19. Attn: [*]

SECTION 20. Re: Second Amended and Restated Loan and Security Agreement dated May 2016 between, among others, (i) UNIQURE BIOPHARMA B.V., and UNIQURE, INC., (hereinafter collectively referred to as "**Borrower**"), the lenders party thereto and HERCULES CAPITAL FUNDING TRUST 2014-1 as agent for itself and the lenders (collectively, "**Lender**") (the "**Agreement**")

SECTION 21. In connection with the above referenced Agreement, Borrower hereby authorizes the Lender to initiate debit entries for the periodic payments due under the Agreement to Borrower's account indicated below. Borrower authorizes the depository institution named below to debit to such account.

DEPOSITORY NAME _____	BRANCH _____
CITY _____	STATE AND ZIP CODE _____
TRANSIT/ABA NUMBER _____	ACCOUNT NUMBER _____

SECTION 22. This authority will remain in full force and effect so long as any amounts are due under the Agreement.

SECTION 23. _____
(Borrower)(Please Print)

By: _____
Date: _____

SCHEDULE 1
LIST OF SUBSIDIARIES

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 1.1
COMMITMENTS

2018 TERM LOAN ADVANCES

LENDER	**TRANCHE**	**COMMITMENT**	**ADVANCES OUTSTANDING AS OF SECOND AMENDMENT CLOSING DATE**
HERCULES CAPITAL, INC.	2018 Term A Loan Advance	$0	$7,000,000
HERCULES CAPITAL FUNDING TRUST 2018-1	2018 Term A Loan Advance	$0	$13,000,000
HERCULES CAPITAL FUNDING TRUST 2019-1	2018 Term A Loan Advance	$0	$15,000,000
TOTAL		$0	$35,000,000

2021 TERM LOAN ADVANCES

LENDER	**COMMITMENT**
HERCULES CAPITAL, INC.	$100,000,000
TOTAL COMMITMENTS	$100,000,000

SECTION 24.

SCHEDULE 1A
INDEBTEDNESS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 1B
INVESTMENTS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 1C
LIENS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.3
CONSENTS, ETC.

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.5
ACTIONS BEFORE GOVERNMENTAL AUTHORITIES

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.8
TAX MATTERS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.9
INTELLECTUAL PROPERTY CLAIMS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.10
INTELLECTUAL PROPERTY

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.11
BORROWER PRODUCTS

[*]

Exhibit A to Amendment No. 2 to Loan and Security Agreement

SCHEDULE 5.14
CAPITALIZATION

Capitalization – see SEC Form 20-F published on 4 April 2016 or Dutch annual accounts

Subsidiaries – see Schedule 1

Exhibit A to Amendment No. 2 to Loan and Security Agreement

Exhibit 21.1

March 1, 2021

SUBSIDIARIES OF UNIQURE N.V.

Name of Subsidiary	Jurisdiction of Organization
uniQure biopharma B.V.	The Netherlands
uniQure IP B.V.	The Netherlands
uniQure Inc.	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors
uniQure N.V.:

We consent to the incorporation by reference in the registration statements (No. 333-225636) on Form S-3 and (No. 333-225629, No. 333-222051, No. 333-218005 and No. 333-197887) on Form S-8 of uniQure N.V. of our report dated March 1, 2021, with respect to the consolidated balance sheets of uniQure N.V. as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, shareholders' equity, and cash flows for the years then ended, and the related notes, and the effectiveness of internal control over financial reporting as of December 31, 2020, which report appears in the 2020 Annual Report on Form 10-K of uniQure N.V. Our report refers to a change in accounting for leases due to the adoption of ASC Topic 842 Leases.

/s/ KPMG Accountants N.V.

Amstelveen, the Netherlands
March 1, 2021

Exhibit 23.2

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-225636) and Form S-8 (No. 333-225629, No. 333-222051, No. 333-218005 and No. 333-197887) of uniQure N.V. of our report dated February 28, 2019 relating to the financial statements, which appears in this Form 10-K.

/s/ R.M.N. Admiraal RA

PricewaterhouseCoopers Accountants N.V.
Amsterdam, the Netherlands

March 1, 2021

Exhibit 31.1

Certification of Chief Executive Officer

I, Matthew Kapusta, certify that:

1. I have reviewed this Annual Report on Form 10-K of uniQure N.V.;

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 registrant as of, and for, the periods presented in this report;

4. The registrant'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 registrant 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 registrant, 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 registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

By: /s/ MATTHEW KAPUSTA

Matthew Kapusta
Chief Executive Officer
March 1, 2021

Exhibit 31.2

Certification of Chief Financial Officer

I, Matthew Kapusta, certify that:

1. I have reviewed this Annual Report on Form 10-K of uniQure N.V.;

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 registrant as of, and for, the periods presented in this report;

4. The registrant'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 registrant 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 registrant, 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 registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

By: /s/ MATTHEW KAPUSTA

Matthew Kapusta
Principal Financial Officer
March 1, 2021

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with this Annual Report of uniQure N.V. (the "Company") on Form 10-K for the period ended December 31, 2020, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Matthew Kapusta, Chief Executive Officer and Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that:

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.

By: /s/ MATTHEW KAPUSTA

Matthew Kapusta
Chief Executive Officer and
Principal Financial Officer
March 1, 2021

A signed original of this written statement required by Section 906 has been provided to uniQure N.V. and will be retained by uniQure N.V. and furnished to the SEC or its staff upon request.