

**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, 2022

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

uniQure N.V.

(Exact name of Registrant as specified in its charter)

The Netherlands

(Jurisdiction of incorporation or organization)

Paasheuvelweg 25,

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.

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements.

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b).

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, 2022 was \$870.2 million, based on the closing price reported as of June 30, 2022 on the Nasdaq Global Select Market.

As of February 23, 2023, the registrant had 46,982,485 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 2023 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than April 30, 2023 and to be delivered to shareholders in connection with the 2023 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Annual Report on Form 10-K.

TABLE OF CONTENTS

	<u>Page</u>
<u>PART I</u>	
	<u>SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS</u>
<u>Item 1</u>	<u>Business</u>
<u>Item 1A</u>	<u>Risk Factors</u>
<u>Item 1B</u>	<u>Unresolved Staff Comments</u>
<u>Item 2</u>	<u>Properties</u>
<u>Item 3</u>	<u>Legal Proceedings</u>
<u>Item 4</u>	<u>Mine Safety Disclosures</u>
<u>PART II</u>	
<u>Item 5</u>	<u>Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>
<u>Item 6</u>	<u>Reserved</u>
<u>Item 7</u>	<u>Management’s Discussion and Analysis of Financial Condition and Results of Operations</u>
<u>Item 7A</u>	<u>Quantitative and Qualitative Disclosures About Market Risk</u>
<u>Item 8</u>	<u>Financial Statements and Supplementary Data</u>
<u>Item 9</u>	<u>Changes in and Disagreements With Accountants on Accounting and Financial Disclosure</u>
<u>Item 9A</u>	<u>Controls and Procedures</u>
<u>Item 9B</u>	<u>Other Information</u>
<u>Item 9C</u>	<u>Disclosure Regarding Foreign Jurisdictions that Prevent Inspections</u>
<u>PART III</u>	
<u>Item 10</u>	<u>Directors, Executive Officers and Corporate Governance</u>
<u>Item 11</u>	<u>Executive Compensation</u>
<u>Item 12</u>	<u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>
<u>Item 13</u>	<u>Certain Relationships and Related Transactions, and Director Independence</u>
<u>Item 14</u>	<u>Principal Accounting Fees and Services</u>
<u>PART IV</u>	
<u>Item 15</u>	<u>Exhibits, Financial Statement Schedules</u>
<u>Item 16</u>	<u>Form 10-K Summary</u>

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, our collaboration and license agreements, 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 I, 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 forward-looking 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

The following is a summary of the principal risks associated with an investment in our ordinary shares:

- We have encountered, and may continue to encounter, delays in, and impediments to the progress of our clinical trials or fail to demonstrate the safety and efficacy of our product candidates.
- We may not be successful in our efforts to use our gene therapy technology platform to build a pipeline of additional product candidates, and we may not be successful in our efforts to create innovative programs, platform technologies or other technologies to be competitive with others.
- We may not be successful in our efforts to in-license or acquire product candidates that align with our research and development strategy, and any such transactions may not achieve the expected cash flows or could result in additional costs and challenges.
- 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.
- 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 also have experienced and could continue to experience increased competition for and compensation expenses associated with employee recruiting and employee retention, which could adversely affect our business.
- 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 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 and other proprietary technology, which could increase the possibility that a competitor will discover them or that our trade secrets and other proprietary technology 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. The amount of capital we will be required to raise will depend in part on a \$75.0 million milestone payment that CSL Behring would owe on occurrence of a first sale of HEMGENIX[®] in the European Union prior to July 2, 2023, as well as the royalties we will receive from sales of HEMGENIX[®].
- Our relationships with employees, customers, and third-parties is subject to applicable laws and regulations, the non-compliance of any of which could 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.
- Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches or other errors or disruptions, which could result in a material disruption of our product development programs, such as potential issues with data integrity or loss of data.
- 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.
- Our business, operations and supply chain have been, and may continue to be, materially and adversely affected by the ongoing Covid pandemic.

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 and seek to deliver to patients suffering from rare and other devastating diseases single treatments with potentially curative results. We are advancing a pipeline of innovative gene therapies, including our clinical candidate for the treatment of Huntington’s disease and amyotrophic lateral sclerosis (“ALS”) as well as preclinical product candidates, including candidates for the treatment of refractory temporal lobe epilepsy (“rTLE”) and Fabry disease. In November 2022 and February 2023, our internally-developed HEMGENIXÔ, a gene therapy for the treatment of hemophilia B, was approved for commercialization by the United States Food and Drug Administration (“FDA”) and the European Medicines Agency (“EMA”), respectively. In June 2020, we agreed to license HEMGENIXÔ to CSL Behring LLC (“CSL Behring”), which is now responsible for the commercialization of HEMGENIXÔ. We are manufacturing HEMGENIXÔ for CSL Behring and are entitled to specific milestone payments and royalties on net sales. 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 collaboration

On June 24, 2020 (the “Signing Date”), uniQure biopharma B.V., a wholly owned subsidiary of uniQure N.V., entered into a commercialization and license agreement (the “CSL Behring Agreement”) with CSL Behring, pursuant to which CSL Behring received exclusive global rights to etranacogene dezaparvovec (the “Product”). The transaction became fully effective in May 2021 (the “Closing”).

In March and April 2022, CSL Behring submitted marketing applications for the Product in the United States (“U.S.”) and European Union (“EU”). In March and April 2022, we received the \$55.0 million owed to us by CSL Behring related to the submission of these marketing applications.

In November 2022, the FDA approved the marketing application for the U.S., and in February 2023 the EMA approved the marketing application for the EU. We are eligible to receive a \$100.0 million payment from CSL Behring following the first sale of the Product in the U.S. We are also eligible to receive a \$75.0 million payment from CSL Behring following the first sale of the Product in any of five major European countries, namely France, Germany, Italy, Spain, and the United Kingdom, provided the first sale occurs prior to July 2, 2023. We recorded the \$100.0 million milestone payment we are eligible to receive from CSL Behring associated with the first sale in the U.S. as license revenue in the year ended December 31, 2022, as we expect this event to occur in 2023. We did not record license revenue related to a \$75.0 million payment in the year ended December 31, 2022, as the accomplishment of this milestone prior to July 2, 2023 is contingent on factors outside our control.

We are eligible to receive up to \$1.3 billion in additional commercial milestones, and tiered double-digit royalties of up to a low-twenties percentage of net product sales arising from the Product.

Huntington’s disease program (AMT-130)

AMT-130 is our novel gene therapy candidate for the treatment of Huntington’s disease.

We are currently conducting a randomized, controlled and blinded Phase I/II clinical trial for AMT-130 in the U.S. The lower-dose cohort of this trial includes 10 patients, of which six patients received treatment with AMT-130 and four patients received imitation surgery. The higher-dose cohort includes 16 patients, of which 10 patients received treatment with AMT-130 and six patients received imitation surgery. Patients receiving imitation surgery have the option to cross over after 12 months if they meet the inclusion criteria for the study. We are also conducting an open-label Phase Ib/II study in the EU, which includes six patients in the lower-dose cohort and nine patients in the higher-dose cohort. All 15 patients in the EU study will receive AMT-130.

On March 21, 2022, we announced that we completed the enrollment of all 26 patients in the first two cohorts of our Phase I/II clinical trial of AMT-130 in the U.S. In July 2022, we began crossing over patients who received the imitation surgical procedure.

On June 23, 2022, we announced safety and biomarker data from the 10 patients enrolled in the low-dose cohort. At 12 months of follow-up on the patients in the low-dose cohort:

- AMT-130 was generally well-tolerated with no serious adverse events related to AMT-130 reported in the treated patients. There were two serious adverse events unrelated to AMT-130, including a deep-vein thrombosis in the elbow of one patient that was resolved with anticoagulants and transient post-operative delirium in the second patient that was resolved through supportive care.
- In the four treated patients with evaluable data, mean levels of mutant Huntingtin protein in the cerebral spinal fluid (“CSF mHTT”) declined at all timepoints compared to baseline, and decreased by 53.8% at 12 months of follow-up (range from 44% decrease to 71% decrease). In the three control patients with evaluable data, mean levels of CSF mHTT showed an increase compared to baseline at one, three, six and nine months of follow-up, and decreased by 16.8% compared at 12 months of follow-up (range 35% increase to 47% decrease).
- In the six treated patients, measurements of neurofilament light chain in the cerebral spinal fluid (“CSF NfL”), a biomarker of neuronal damage, initially increased as expected following the AMT-130 surgical procedure and declined thereafter, nearing baseline at 12 months of follow-up. At 12 months, mean CSF NfL showed an 8% increase compared to baseline (range 46% increase to 14% decrease). Two of the six treated patients were at or below baseline at 12 months of follow-up, with an additional patient below baseline at 15 and 18 months of follow-up. In the four control patients, mean CSF NfL remained stable or slightly declined over 12 months (range 1% increase to 35% decrease).

Also on June 23, 2022, we announced that 10 patients in our Phase Ib/II study in the EU had been treated with AMT-130.

In August 2022, we announced a voluntary postponement of AMT-130 higher-dose procedures due to suspected unexpected severe adverse reactions (“SUSARs”) reported in three of the 14 patients that were treated with the higher dose of AMT-130. In October 2022, after completing a comprehensive safety investigation, the Data Safety Monitoring Board (“DSMB”) recommended resuming treatment at the higher dose of AMT-130 for the remaining five European patients and any patients in the U.S. trial eligible to cross over from the control arm to the treatment. All three patients have experienced full resolution of the reported SUSARs.

Preclinical programs

In May 2022, we presented certain preclinical findings on our gene therapy candidates for refractory temporal lobe epilepsy, Fabry disease, Parkinson’s disease, Amyotrophic lateral sclerosis, and Alzheimer’s disease at the American Society of Gene and Cell Therapy Hybrid Congress.

In July and August 2022, respectively, we initiated Investigational New Drug-enabling (“IND-enabling”), Good Laboratory Practice (“GLP”) toxicology studies in non-human primates for our gene therapy candidates in rTLE and Fabry disease.

In November 2022, we hosted a virtual investor event focused on the target candidate for the treatment of temporal lobe epilepsy (“AMT-260”). The presentation highlighted preclinical data on AMT-260 and our initial plans for clinical development, as well as our miQURE™ and linQURE™ technology platforms that utilize micro ribonucleic acids (“miRNAs”) to reduce the expression of abhorrent genes. We also highlighted our progress in developing a commercial-scale AAV manufacturing platform.

Termination of Bristol-Myers Squibb Agreement

We entered into a collaboration and license agreement with Bristol-Myers Squibb (“BMS”) in May 2015 (“BMS CLA”). BMS had initially designated four Collaboration Targets in 2015. 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 (the “Amended BMS CLA”). The Amended BMS CLA did not extend the initial research term, and BMS did not replace any of the active Collaboration Targets.

On November 21, 2022, we received written notice that BMS was terminating the BMS CLA as amended (“Termination Notice”), effective on February 21, 2023 (“Termination Date”). As a result of the termination of the BMS CLA, the contractually defined payment set for in the Amended BMS CLA that would have required us to make a payment to BMS in the event of a change of control transaction is of no further force or effect.

The Investor Agreement dated April 2015 between the Company and BMS remains in force according to its terms, but various provisions of the Investor Agreement have been terminated.

Amyotrophic Lateral Sclerosis (AMT-162)

On January 31, 2023, we announced that we have entered into a global licensing agreement for a one-time, intrathecally administered gene therapy for ALS with Apic Bio. With this agreement, we have added to our pipeline of gene therapies to treat neurological disorders. We made an initial cash payment of \$10.0 million. In addition, we will pay Apic Bio up to \$43.0 million in milestones upon achievement of regulatory approvals in the U.S. and Europe and pre-specified annual net sales, and a tiered royalty on net sales ranging from the mid-single digits to low double digits.

Our Mission and Strategy

Our mission is to deliver curative, one-time administered genomic medicines that transform the lives of patients. We aim to build an industry-leading, fully integrated, and global company that leverages its technology and proprietary manufacturing platform to deliver these medicines to patients with serious unmet medical needs.

Our strategy to achieve this mission is to:

Advance the development of AMT-130, a potential one-time gene-therapy approach for the treatment of Huntington’s disease. AMT-130 is the first AAV-based gene therapy to enter clinical development for Huntington’s disease. It consists of an AAV5 vector carrying an artificial miRNA specifically tailored to silence the huntingtin gene and leverages our proprietary miQURE™ silencing technology. The therapeutic goal of AMT-130 is to inhibit the production of the mutant HTT protein. In June 2022, we announced initial data from patients in the lower-dose cohort of the U.S. Phase I/II study. Patient enrollment is ongoing in the U.S. Phase I/II study as well as an EU Phase Ib/II study.

Support the commercialization and global expansion of HEMGENIXÔ. HEMGENIXÔ is an FDA and EMA approved one-time administered gene therapy for the treatment of patients with severe and moderately severe hemophilia B. In 2020 we licensed the commercial rights to HEMGENIXÔ to CSL Behring. We will be supplying CSL Behring with HEMGENIXÔ for a number of years. We are eligible to receive up to \$1.3 billion in additional commercial milestones, and tiered double-digit royalties of up to a low-twenties percentage of net product sales arising from HEMGENIXÔ.

Advance our pipeline of other preclinical and clinical-stage gene therapy candidates into first-in-human trials. We expect to advance additional one-time administered gene therapy product candidates into clinical studies, including AMT-260 for the treatment of rTLE, AMT-162 for the treatment of superoxide dismutase 1 (“SOD1”)-ALS, and AMT-191 for the treatment of Fabry disease. AMT-260 and AMT-162 utilize an AAV9 vector to deliver customized miRNAs to suppress the expression of the glutamate inotropic receptor kainate type subunit 2 (“GRIK2”) and SOD1 genes, respectively. AMT-191 is an AAV5 gene therapy incorporating the α -galactosidase A (“GLA”) transgene.

Initiate additional gene therapy programs leveraging validated technologies and focused on central-nervous system (“CNS”) and other debilitating disorders. We are leveraging proven enabling technologies, including AAV vectors, promoters, and manufacturing capabilities, to develop gene therapies that have the potential to be best or first-in-class. Many of our gene therapy product candidates incorporate AAV5 or AAV9 vectors, which are currently being utilized in commercially available, approved gene therapies, as well as extensively studied in the clinical setting. We believe AAV5 may potentially offer a favorable immunogenicity profile and the ability to confer therapeutic effect in patients with pre-existing antibodies. We have also developed substantial know-how around optimizing delivery of gene therapies to the central nervous system and the liver, which can be leveraged across multiple product candidates.

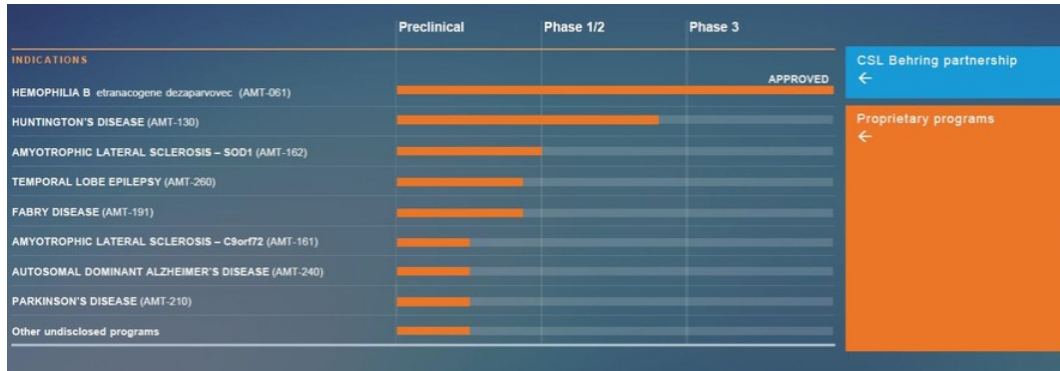
Maintain our leadership position in commercial-scale AAV manufacturing. We have established cGMP, commercial-scale manufacturing capabilities for AAV-based gene therapies in our commercially-licensed Lexington, Massachusetts facility and completed construction of a second cGMP manufacturing facility in Amsterdam, the Netherlands that complements our work in Lexington. 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.

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 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 next-generation delivery approaches, such as smart AAV capsids potentially capable of improved CNS transduction and crossing the blood-brain barrier, as well as novel cargo technologies such as miQURE, our one-time administered gene silencing platform. We are expanding our cargo platforms to include additional technologies, such as linkQURE to combine multiple miRNAs to suppress different genes, goQURE for simultaneous silencing of a disease gene and replacement with a healthy gene, and abQURE for the delivery of therapeutic antibodies. We are also developing novel administration approaches, such as QUREDose, to enable dosing through neutralizing antibodies and re-dosing. These various 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; (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 (HEMGENIX™ or etranacogene dezaparvovec)

Hemophilia B Disease and Market Background

Hemophilia B is a rare, lifelong bleeding disorder caused by a single gene defect, resulting in insufficient production of factor IX, a protein primarily produced by the liver that helps blood clots form. Treatments for moderate to severe hemophilia B include prophylactic infusions of factor IX replacement therapy to temporarily replace or supplement low levels of blood-clotting factor and, while these therapies are effective, those with hemophilia B must adhere to strict, lifelong infusion schedules. They may also still experience spontaneous bleeding episodes as well as limited mobility, joint damage or severe pain as a result of the disease. For appropriate patients, HEMGENIX™ allows people living with hemophilia B to produce their own factor IX, which can lower the risk of bleeding.

CSL Behring collaboration

On June 24, 2020, we entered into the CSL Behring Agreement pursuant to which CSL Behring received exclusive global rights to HEMGENIX™. The transaction became fully effective on May 6, 2021, one day after the waiting period under the HSR Act expired on May 5, 2021.

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.

In March and April 2022, we received the total \$55.0 million owed to us by CSL Behring related to CSL Behring's submissions of marketing applications for HEMGENIX™ in the EU in March 2022 and the U.S. in April 2022.

In November 2022 the FDA approved the marketing application for the U.S. and in February 2023 the EMA approved the marketing application for the EU. We are eligible to receive a \$100.0 million payment from CSL Behring following the first sale of the Product in the U.S. We are also eligible to receive a \$75.0 million payment from CSL Behring following the first sale of the Product in any of five major European countries, namely France, Germany, Italy, Spain, and the United Kingdom, provided the first sale occurs prior to July 2, 2023. We recorded the \$100.0 million payment associated with the first sale in the U.S. as license revenue in the year ended December 31, 2022 as we expect this event to occur in 2023. We did not record license revenue related to a \$75.0 million payment in the year ended December 31, 2022, as the accomplishment of this milestone prior to July 2, 2023 is contingent on factors outside our control.

We and CSL Behring also entered into a development and commercial supply agreement, pursuant to which, among other things, we will supply the Product to CSL Behring. We are contractually obligated to supply the Product until such time that these capabilities are transferred to CSL Behring or its designated contract manufacturing organization. On September 6, 2022, CSL Behring notified us of its intent to transfer manufacturing technology in the coming years related to HEMGENIX™ to a third-party contract manufacturer designated by CSL Behring. CSL Behring also informed us of its intent to retain us as a source for manufacturing after the completion of the technology transfer.

Development of HEMGENIX™ (etranacogene dezaparvovec) for Hemophilia B

HEMGENIX™ is approved for adults 18 years or older with hemophilia B who currently use factor IX prophylaxis therapy or have current or historical life-threatening hemorrhage or have repeated, serious spontaneous bleeding episodes. HEMGENIX™ includes an AAV5 vector incorporating the FIX-Padua variant ("FIX-Padua"). The product 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.

The approvals were based in part on data from our Phase III HOPE-B pivotal trial to evaluate the safety and efficacy of HEMGENIX™. In the open-label, single arm, HOPE-B study, 54 adult male hemophilia B patients with severe or moderately severe hemophilia B, with or without pre-existing AAV5 neutralizing antibodies, were infused with a single dose of HEMGENIX™. HEMGENIX™ produced mean factor IX activity of 39.0 IU/dL at six months and 36.9 IU/dL at 18 months post infusion, which was sustained at 36.7 IU/dL in the long-term follow-up data at two years. In addition, 94 percent (51 out of 54) of patients treated with HEMGENIX™ discontinued use of prophylaxis and remained free of previous continuous routine prophylaxis therapy.

The data demonstrate the annualized bleeding rate ("ABR") for all bleeds was reduced by 64% during months 7-24 of the study (mean ABR 1.51 vs. 4.18 during the lead-in period; p=0.0002), sustaining the same bleed reduction that satisfied the study's primary endpoint. The FDA-approved prescribing information for HEMGENIX™ shows that ABR for all bleeds was reduced by 54% during months 7-18 of the study. Treatment with HEMGENIX™ also reduced mean unadjusted annualized factor IX consumption by 96% from the lead-in period (257,339 IU/year/participant) to months 19-24 (9751 IU/year/participant; p<0.0001).

Of the 557 treatment-emergent adverse events reported 24-months post-infusion, 424 (76%) were mild, 115 (21%) were moderate and 18 (3%) were severe. A total of 38 participants (70.4%) experienced 93 treatment-related adverse events, with only one occurring during months 18-24. There were no serious adverse effects related to treatment and the most common side effects (incidence $\geq 5\%$) were liver enzyme elevations, headache, elevated levels of a certain blood enzyme, flu-like symptoms, infusion-related reactions, fatigue, nausea and feeling unwell.

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, (the “‘405 Patent”). The ‘405 Patent was subject to *Inter Partes Review* (“IPR”) proceedings at the Patent Trials and Appeal Board (“PTAB”) of the United States Patent & Trademark Office (“USPTO”). Ultimately, the challenged claims of the ‘405 Patent were withdrawn but the unchanged claims remain in force. The ‘405 Patent thus covers compositions of FIX-Padua polypeptides (proteins), their therapeutic uses as well as nucleic acid sequences encoding FIX-Padua. The FIX Padua variant is a FIX protein carrying a leucine at the R338 position, often called the “FIX-Padua” or “Padua mutant.”

On May 29, 2018, the 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.

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 October 14, 2022, Pfizer filed a Statement of Claim at the Federal Court in Canada to impeach our Canadian Patent CA 2,737,094. We are currently defending this case.

On December 28, 2022, the European Patent Office granted Patent Number EP 3581650, which covers FIX-Padua nucleic acids and its uses in gene therapy. That same day, Pfizer filed a Claim at the UK High Court, Patent Court seeking revocation of the UK part of EP 3581650. We are currently defending this case.

Both in the U.S. and in Europe, we have pending divisional applications still in prosecution phases.

On May 11, 2021, Pfizer, Inc. filed three petitions at the USPTO seeking *Inter Partes Review* of U.S. Patent Nos. 9,982,248 (the “‘248 Patent”) and 10,465,180 (the “‘180 Patent”) and together with the ‘248 Patent, the “Patents”). On November 15, 2022, the PTAB issued three Final Written Decisions (“FWD”) finding the claims of the challenged patents invalid. On January 17, 2023, Notices of Appeal were filed at the Court of Appeal of the Federal Circuit (“CAFC”) contesting these FWDs.

Fabry disease program (AMT-191)

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 and approximately one in 20,000 females. 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-191 for Fabry Disease

In September 2020, we selected a lead gene therapy candidate (AMT-191) for the treatment of Fabry disease. 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-191 demonstrated the most robust and sustained increases in GLA activity and subsequent functional improvement.

In October 2021, we presented preclinical data for AMT-191 at the European Society of Gene and Cell Therapy (“ESGCT”), confirming efficiency and cross correction in a Fabry mouse model, with increased gamma-linolenic acid in the liver, kidney, heart, and brain and normalized lysoglobotriaosylceramide-3 levels in main target organs.

In August 2022, we initiated IND-enabling, GLP toxicology studies in non-human primates for our lead candidate.

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 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 a miRNA specifically designed to silence the huntingtin gene and the potentially highly toxic exon 1 protein fragment. We are currently conducting a Phase I/II clinical trial for AMT-130 in the U.S. and a Phase Ib/II study in the EU. Together, these studies are intended to establish safety, proof of concept, and the optimal dose of AMT-130 to take forward into Phase III development or into a confirmatory study should an accelerated registration pathway be feasible. AMT-130 has received Orphan Drug and Fast Track designations from the FDA and Orphan Medicinal Product Designation from the EMA.

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.

On March 21, 2022, we announced that we completed the enrollment of all 26 patients in the first two cohorts of our randomized, double-blinded, Phase I/II clinical trial of AMT-130 taking place in the U.S. In the study, patients are randomized to either treatment with AMT-130 or to an imitation surgical procedure. The treated patients have received a single administration of AMT-130 using MRI-guided, convection-enhanced stereotactic neurosurgical delivery directly into the striatum (caudate and putamen). The trial consists of a blinded 12-month period followed by unblinded long-term follow-up for five years. The lower-dose cohort includes 10 patients, of which six patients received treatment with AMT-130 and four patients received imitation surgery between June 19, 2020 and April 5, 2021. The higher-dose cohort includes 16 patients, of which 10 patients received treatment with AMT-130 and six patients received imitation surgery between June 13, 2021 and March 21, 2022. In July 2022, we initiated dosing in patients crossing over from the imitation surgical procedure arm to treatment. A third cohort, which will include up to 18 additional randomized patients receiving the higher dose, is intended to explore the use of alternative stereotactic navigation systems to simplify placement of catheters for infusions of AMT-130.

On June 23, 2022, we announced safety and biomarker data from the 10 patients enrolled in the lower-dose cohort. At 12 months of follow-up on the patients in the lower-dose cohort:

- AMT-130 was generally well-tolerated with no serious adverse events related to AMT-130 reported in the treated patients. There were two serious adverse events unrelated to AMT-130, including a deep-vein thrombosis in the elbow of one patient that was resolved with anticoagulants and transient post-operative delirium in the second patient that was resolved through supportive care.
- In the four treated patients with evaluable data, mean levels of CSF mHTT declined at all timepoints compared to baseline and decreased by 53.8% at 12 months of follow-up (range 44% decrease to 71% decrease). In the three control patients with evaluable data, mean levels of CSF mHTT showed an increase compared to baseline at one, three, six and nine months of follow-up, and decreased by 16.8% compared at 12 months of follow-up (range 35% increase to 47% decrease).
- In the six treated patients, measurements of CSF NfL, a biomarker of neuronal damage, initially increased as expected following the AMT-130 surgical procedure and declined thereafter, nearing baseline at 12 months of follow-up. At 12 months, mean CSF NfL showed an 8% increase compared to baseline (range 46% increase to 14% decrease). Two of the six treated patients were at or below baseline at 12 months of follow-up, with an additional patient below baseline at 15 and 18 months of follow-up. In the four control patients, mean CSF NfL remained stable or slightly declined over 12 months (range 1% increase to 35% decrease).

On June 23, 2022, we announced that in our open-label, Phase Ib/II study in the EU all six patients in the lower-dose cohort and five out of the nine patients in the higher-dose cohort had been treated with AMT-130.

In August 2022, we announced a voluntary postponement of AMT-130 higher-dose procedures due to SUSARs reported in three of the 14 patients that were treated with the higher dose of AMT-130. Two patients experienced localized inflammatory responses and related symptoms shortly after the procedure, while the third patient experienced severe headaches and other related symptoms. In October 2022, after completing a comprehensive safety investigation, the DSMB recommended resuming treatment at the higher dose of AMT-130 for the remaining five European patients and any patients in the U.S. trial who are eligible to cross over from the control arm to the treatment. All three patients have experienced full resolution of the reported SUSARs.

We have added additional risk mitigation procedures including closer patient monitoring during the first two weeks after the administration of AMT-130 and a seven-day, post-surgical in-person visit. The DSMB recommended that the use of immunosuppression remain at the discretion of the treating physician.

Temporal Lobe Epilepsy Program (AMT-260)

Temporal Lobe Epilepsy Disease and Market Background

TLE affects approximately 1.3 million people in the U.S. and EU alone, of which approximately 0.8 million patients are unable to adequately control acute seizures with currently approved anti-epileptic therapies. Patients with refractory TLE experience increased morbidity, excess mortality, and poor quality of life.

Our Development of AMT-260 for Temporal Lobe Epilepsy

In July 2021, we acquired Corlieve Therapeutics (“Corlieve”) and its lead program, now known as AMT-260, to treat temporal lobe epilepsy. AMT-260 is being developed based on exclusive licenses to certain patents Corlieve obtained in 2020 from two French research institutions that continue to collaborate with us.

AMT-260 is a gene therapy using an AAV9 vector. The use of AAV9 to deliver any sequence that affects the expression of the GRIK2 gene in humans has been exclusively licensed from Regenxbio Inc (“Regenxbio”). Regenxbio provides contractually agreed research and development services up to the transfer of manufacturing activities to a designated contract manufacturer.

AMT-260, employs miRNA silencing technology to target suppression of aberrantly expressed GluK2 containing kainate receptors in the hippocampus of patients with rTLE.

In October 2021, we presented preclinical data for AMT-260 at the ESGCT. AMT-260 reduces the expression of GluK2 in cortical neurons, reduces epileptiform activity and hyperlocomotion in a preclinical model of epilepsy and blocks epileptiform discharges in organotypic slices from patients with TLE.

In July 2022, we initiated IND-enabling, GLP toxicology studies in non-human primates for our gene therapy candidate in rTLE.

Parkinson’s Disease (AMT-210)

AMT-210 is our preclinical product candidate for the treatment of α -synucleinopathies, a group of neurodegenerative diseases characterized by anormal accumulation of insoluble α -synuclein in neurons and glial cells, including Parkinson’s disease, dementia with Lewy bodies and multiple systems atrophy. Although varying in prevalence, symptom patterns, and severity among disorders, all α -synucleinopathies have in common the loss of neurons that affects longevity and quality of life.

AMT-210 is a one-time, brain-target AAV gene therapy incorporating uniQure’s miQURE gene silencing technology. It is designed to reduce the amount of misfolded alpha-synuclein protein and subsequent fibril formation in patients with familial and sporadic disease.

Alzheimer’s Disease (AMT-240)

AMT-240 is our preclinical product candidate for the treatment autosomal dominant Alzheimer’s disease. Alzheimer’s disease causes loss of memory and dementia and is the most common neurodegenerative disease. Human genetic studies suggest that the Apolipoprotein E (APOE) gene is an important factor in the pathogenesis of Alzheimer’s disease. APOE consists of 3 major isoforms that are structurally and functionally different. The APOE4 isoform is associated with earlier onset of Alzheimer’s disease while APOE2 and variants of APOE3 are protective.

AMT-240 is a one-time gene therapy using uniQure’s miQURE gene-silencing technology to silence the toxic APOE4 variant while expressing a protective APOE variant. It is initially targeted as a treatment for autosomal dominant Alzheimer’s disease patients but may be effective for a broader population of patients.

Amyotrophic Lateral Sclerosis Caused by Mutations in C9ORF72 (AMT-161)

AMT-161 is our preclinical product candidate that uses our miQURE gene silencing technology to target a toxic allele of C9ORF72 as a potential treatment for ALS.

ALS is caused by degeneration of upper and lower motor neurons, resulting in muscle weakness and atrophy. This rapid progressive loss of motor neurons typically starts at mid-life and progresses over the course of 2-8 years, leading to loss of movement and death.

About 20% of ALS has a genetic cause. The most common genetic mutation that causes ALS is a G4C2 hexanucleotide repeat expansion in the C9ORF72 gene. The hexanucleotide expansion causes the formation of ribonucleic acid (“RNA”) aggregates and the production of toxic dipeptides that ultimately lead to neuronal death. AMT-161 is a one-time, intrathecally-administered AAV gene therapy that targets the repeat-expanded C9ORF72 allele to lower toxic RNA aggregates and prevent dipeptide protein formation.

Amyotrophic Lateral Sclerosis caused by mutations in SOD1(AMT-162)

On January 31, 2023, we announced that we entered into a global licensing agreement with Apic Bio for a novel, one-time, intrathecally administered gene therapy for ALS caused by mutations in superoxide dismutase 1 (“SOD1”), a rapidly progressing, rare motor neuron disease that leads to loss of everyday functions and is uniformly fatal (previously known as APB-102). With this agreement, we have added AMT-162 to our pipeline of gene therapies to treat neurological disorders. The FDA has cleared the investigational new drug application for APB-102 and has granted Orphan Drug and Fast Track designation. Mutations in the SOD1 gene of ALS account for approximately one-fifth of all inherited forms of this fatal disease. APB-102 is comprised of a recombinant AAVrh10 vector that expresses a miRNA designed to knock down the expression of SOD1 with the goal of slowing down or potentially reversing the progression of ALS in patients with SOD1 mutations. We plan to initiate a Phase I/II trial of AMT-162 in the second half of 2023.

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 deoxyribonucleic acid (“DNA”); (ii) the cargo, including the transgene or therapeutic gene, and promoters, or the DNA sequence that drives the expression of the transgene; and (iii) administration techniques.

We dedicate significant effort to designing and screening novel AAV capsids with the potential for (i) higher biological potency; (ii) improved biodistribution including greater cell transduction and increased cellular specificity; and (iii) enhanced safety. We believe we have significant expertise in vector engineering and have created promising genetically engineered capsids using both rational and directed evolution approaches.

We also work on designing synthetic promoters that enable high levels of tissue or disease specific gene expression. A “promoter” is an essential component of a gene therapy construct that controls expression of a therapeutic protein. Synthetic promoters, that do not exist in nature, are optimally tailored to drive gene expression at a desired level and specificity.

To further tailor and optimize gene therapies to 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 are developing methods for delivering multiple doses of a gene therapy to a patient using a combination of immune modulation and antibody neutralization. The ability to deliver multiple doses of an AAV to a patient could potentially increase our ability to deliver the correct dose of a virus to a patient and might enable us to re-administer our gene therapies to patients that have lost expression of a transgene.

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. With the exception of AMT-260 we produce our gene therapies either at our Amsterdam, the Netherlands or our commercially-licensed, 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. With the exception of AMT-260 and AMT-161 programs, 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.
- (4) *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.
- (5) *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 U.S., 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 U.S. 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 U.S.. 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, 2022, our intellectual property portfolio included 120 issued patents (including 30 U.S. patents and 14 patents granted by the European Patent Office (“EPO”)) and 160 pending patent applications (including 29 U.S. patent applications and 36 EPO patent applications).

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 Programs

Hemophilia B (AMT-061)

We own a patent family, including patents and patent applications, directed to the use of the Padua mutation in human Factor IX (“hFIX”) for gene therapy in etranacogene dezaparvovec.

Huntington’s disease (AMT-130)

We own two patent families directed to gene therapy treatment of Huntington’s disease, including with AMT-130. This miQURE gene silencing technology platform is designed to degrade disease-causing genes, without off-target toxicity, and induce silencing of the entire target organ through secondary exosome-mediated delivery.

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. Under the amended license agreement CSHL granted to us an exclusive license to develop and commercialize therapeutic products for the additional disease classifications in the Field of liver diseases, neuromuscular diseases, and cardiovascular diseases and we have subsequently added such products to our pipeline.

Under this license agreement, as amended, 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

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 rights, 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 have provided Dr. Simioni with an initial license fee and reimbursement of past expenses. Under the agreement, additional payments may come due upon the achievement of certain milestone events related to the development of the Padua IP or as 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 Children’s Research Hospital (“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. With respect to our collaboration with CSL Behring, we have agreed with St. Jude on an apportionment of certain amounts we receive from CSL Behring as sublicensing revenue that is equivalent to a low-single digit percentage of such amounts.

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.

Temporal Lobe Epilepsy

Regenxbio

In June 2020, Corlieve entered into an agreement, subsequently amended in June 2021, with Regenxbio for an exclusive (in the field of using AAV9 to expression of the *GRIK2* gene in humans (the “Field”)), sublicensable, royalty-bearing, worldwide license under Regenxbio’s interest in EU patent application 19185533.7 (the “Foreground Patents”) and related patents, as well as patents covering inventions developed during the collaboration and certain patents and know-how relating to AAV9. The license also includes non-exclusive rights to exploit the licensed Foreground Patents and certain related patents know-how developed in collaboration pursuant to the license agreement outside the Field. The license also includes retained and license back rights that permit Regenxbio and its upstream licensors to exploit for any research, development, commercialization, or other purposes certain patents, inventions and know-how (other than the Foreground Patents) subject to or created pursuant to the license agreement.

Payment obligations under the agreement provide for royalty payments on net sales in the mid-single digit to low-double digits, and milestone payments to Regenxbio in the mid-tens of millions of dollars related to clinical trials, commercialization, and net sales. The agreement also calls for sublicense fees in the low-double digit range. The royalty is paid on sales of license products using any of licensed patents or know-how for as long as the agreement is in effect. Royalty and milestone payments may continue to be owed under the license following termination of the agreement if licensed products are sold following termination of the license. Under the agreement, Corlieve has certain diligence obligations and Regenxbio has certain obligations related to the pre-clinical development of manufacturing technology.

Inserm Transfert

In January 2020, Corlieve entered into license agreement with Inserm Transfert SA (also acting as a delegate for the French National Institute of Health and Medical Research) and La société SATT Aquitaine (the counterparties collectively referred to as “Inserm Transfert”). Under the license agreement, Corlieve is granted an exclusive, sublicensable, royalty-bearing, worldwide license under European Patent (“EP”) patent application 13306265.3 in the field of the prevention and treatment of epilepsy, and in Inserm Transfert’s share in EP patent application 19185533.7 (which is co-owned by Regenxbio) in the field of all human use. Corlieve also is granted a non-exclusive, sublicensable, royalty-bearing, worldwide license under certain know-how in the fields that may be developed by Inserm pursuant to the agreements. Under the agreements, Inserm retains certain rights for teaching, academic and/or research purposes.

Payment obligations under the agreements include a royalty on the net sales of license products in the low single digits, milestone payments associated with clinical trial and regulatory approval milestones of multiple licensed products totaling in the low-single digit millions of Euros. The agreement also calls for sublicense fees in the low to mid double-digit range depending on the timing of such sublicense. The obligation to pay royalties extends until the later of the expiration of the patent rights, any regulatory exclusivity period, and 10 years from the first commercial sale of a licensed product.

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 U.S. and the EU. 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 face worldwide competition from larger pharmaceutical companies, specialty pharmaceutical companies and biotechnology firms, universities and other research institutions and government agencies that are developing and commercializing pharmaceutical products. Our key competitors focused on developing therapies in various indications, include among others, Pfizer, Freeline Therapeutics, Intellia Therapeutics, Sangamo Biosciences, Voyager Therapeutics, Passage Bio, Roche, PTC Therapeutics, Prilenia Therapeutics, CombiGene, Caritas Therapeutics, Alnylam, Wave Life Sciences, Bayer AG, Amicus Therapeutics and 4D Molecular Therapeutics.

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 U.S., EU and other countries extensively regulate, among other things, the approval, research, development, nonclinical 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 U.S. and the EU, 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, civil penalties, 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 U.S., 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. Executive actions have also been issued to encourage domestic manufacturing and the Consolidated Appropriations Act, 2023, was passed at the end of 2022, which included a number of updates to the FDCA. FDA has 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 U.S. must typically undertake the following:

- completion of nonclinical 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 U.S.;
- approval by an independent institutional review board (“IRB”) and, for some studies, 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 cGCP to establish substantial evidence of the safety and efficacy for 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 or remote regulatory assessments 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 U.S. or under an IND, investigational product sponsors must first complete nonclinical studies. Nonclinical 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 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. Special clinical trial ethical considerations also must be taken into account if a study involves children. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of an IND. Sponsors must also provide FDA with diversity action plans. INDs include nonclinical 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 U.S. 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. 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 may 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.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor that regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of the trial. This group may also review interim data to assess the continuing validity and scientific merit of the clinical trial. This group receives special access to unblinded data during the clinical trial and may advise the sponsor to halt, pause, or otherwise modify the clinical trial.

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. 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.

Recent legislation further established a new program that may be used to facilitate future marketing applications and development programs following a first product approval. Specifically, the Consolidated Appropriations Act, 2023 established a program whereby a platform technology that is incorporated within or utilized by an approved drug or biologic product may be designated as a platform technology, provided that certain conditions are met, in which case development and approval of subsequent products using such technology may be expedited.

In addition, under the Pediatric Research Equity Act (the “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 U.S. are also subject to regulation by the FDA. Further, the export of investigational products outside of the U.S. 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 nonclinical 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.

Regulation and FDA Guidance Governing Gene Therapy Products

The FDA has and continues to issue various guidance documents with respect to the development and commercialization of gene therapies. These include guidance on, among other things, the proper preclinical and nonclinical assessment of gene therapies; the chemistry, manufacturing, and controls; the design and conduct of clinical trials; 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. The FDA has also issued guidance documents specific to gene therapies during the COVID-19 public health emergency, including one on manufacturing considerations and the conduct of risk assessments. FDA has further issued guidance focused on the development of gene therapies for the treatment of neurodegenerative diseases, rare diseases, and hemophilia, as such products may face special challenges.

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.

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 and remote regulatory assessments 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. By the date of approval of an accelerated approval product, FDA must specify the conditions for the required post approval studies, including enrollment targets, the study protocol, milestones, and target completion dates. FDA may also require that the confirmatory Phase 4 studies be commenced prior to FDA granting a product accelerated approval. Reports on the progress of the required Phase 4 confirmatory studies must be submitted to FDA every 180 days after approval. 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 using a statutorily defined streamlined process. Failure to conduct the required Phase 4 confirmatory studies or to conduct such studies with due diligence, as well as failure to submit the required update reports can subject a sponsor to penalties.. All promotional materials for drug or biologic candidates approved under accelerated regulations are subject to prior review by the FDA. In recent years, the accelerated approval pathway has come under significant FDA and public scrutiny. Accordingly, the FDA may be more conservative in granting accelerated approval or, if granted, may be more apt to withdrawal approval if clinical benefit is not confirmed. FDA may also require that the confirmatory Phase 4 study be commenced prior to FDA granting a product accelerated approval.

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 nonclinical 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, though 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. 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 or to consider additional information submitted during the application review period. 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 or conduct remote regulatory assessments of the facility or facilities where the product is manufactured. 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 or conduct remote regulatory assessments one or more clinical trial sites to assure compliance with good clinical practices ("GCPs").

After evaluating the marketing application and all related information, including the advisory committee recommendation, if any, and inspection and remote regulatory 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 4 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 healthcare 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 BPCIA, 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 following approval of the reference product. 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 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.

The FDA maintains a list of approved biological products, which is commonly referred to as the Purple Book. This list includes product names, the date of licensure, and any periods of regulatory exclusivity. Following the exchange of patent information between the biosimilar and reference product sponsor, the reference product sponsor must also provide the exchanged patent information and patent expiry dates to the FDA. The FDA then publishes this information in the Purple Book.

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, 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.

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 U.S., or more in cases in which there is no reasonable expectation that the cost of developing and making a biological product available in the U.S. 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. With respect to gene therapies, the FDA has issued a specific guidance on how the agency interprets its sameness regulations. Specifically, whether two products are deemed to be the same by the FDA will depend on the products' transgene expression, viral vectors groups and variants, and additional product features that may contribute to therapeutic effect. Minor product differences will not, generally, result in a finding that two products are different and there are some factors that FDA will consider on a case by case basis. 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.

If a product with orphan designation receives the first FDA approval, it may 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. Notably, a 2021 judicial decision, *Catalyst Pharms., Inc. v. Becerra*, challenged and reversed an FDA decision on the scope of orphan product exclusivity for the drug, Firdapse. Under this decision, orphan drug exclusivity for Firdapse blocked approval of another company's application for the same drug for the entire disease or condition for which orphan drug designation was granted, not just the disease or condition for which approval was received. In a January 2023 Federal Register notice, however, FDA stated that it intends to continue to apply its regulations tying the scope of orphan-drug exclusivity to the uses or indications for which a drug is approved. The exact scope of orphan drug exclusivity will likely be an evolving area.

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 reference biologic exclusivity. 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 designation request 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 an 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 remaining FDA general controls, 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. A de novo request may be used for devices not previously classified by the FDA (and hence are automatically Class III) but are low or moderate risk (due to the application of special controls) and thus are 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 provided that certain criteria are met. 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 that have been 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 fines 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 procurement and non-procurement programs, 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 products. Certain reporting related to samples is also required under federal and state laws and regulations, some of which 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 and will be required to allow interoperable electronic product tracing at the package level by November 2023. Sponsors must also verify that purchasers of the sponsors' products are appropriately licensed. Further, under this legislation, manufacturers have product verification responsibilities, as well as investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products that would result in serious adverse health consequences or 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 also 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, consent decrees, corporate integrity agreements, suspension and debarment from government procurement and non-procurement programs, refusal of orders under existing government contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, civil penalties, criminal prosecution, 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 U.S. 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.

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 is a criminal statute that 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. 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 the one hand and prescribers, purchasers, and formulary managers on the other. The Beneficiary Inducement Civil Monetary Penalties Law imposes similar restrictions on interactions between the biopharmaceutical industry and federal healthcare program beneficiaries. There are certain statutory exceptions and regulatory safe harbors to the Anti-Kickback Statute 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 or reward 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.

Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce or reward referrals of federal healthcare program 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 reimbursement submitted to a federal healthcare program for payment of items or services resulting from such violation constitutes a per se false or fraudulent claim for purposes of the federal civil False Claims Act. 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, 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 PBM, will not be protected under the Anti-Kickback Statute discount safe harbor. Recent legislation delayed implementation of this portion of the rule until January 1, 2026, and further proposed legislation would permanently prohibit implementation of the rule beginning in 2026.

The federal civil False Claims Act prohibits 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 for 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 damages, penalties 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 tens and even hundreds of 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, civil judgment for violating the FCA may result in exclusion from federal healthcare programs, suspension and debarment from government procurement and non-procurement programs, and refusal of orders under existing government contracts. The majority of states also have statutes similar to the federal Anti-Kickback Statute and civil False Claims Act, 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 Law is another potential statute under which biopharmaceutical companies may be subject to enforcement. Among other things, the civil monetary penalties statute 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 manufacturer 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 certain products, including those approved under a BLA (including biosimilars), the Veterans Health Care Act (the “VHCA”) requires sponsors to calculate and report to the Department of Veterans Affairs (“VA”) a different price called the Non-Federal Average Manufacturer 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, 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 healthcare benefits, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare 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 certain payments and other transfers of value made to or at the request of covered recipients, which are physicians (as defined under the Social Security Act), physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives licensed in the U.S. and U.S. teaching hospitals, as well as ownership and investment interests held by physicians and members of their immediate family. Payments made to principal investigators and research institutions at teaching hospitals 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 and organizations. State legislation may also prohibit gifts and 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 certain individually identifiable health information known as protected health information. Among other things, the HITECH Act, and its implementing regulations, made HIPAA’s security standards and certain privacy standards directly applicable to business associates, defined as persons or organizations, other than members of a covered entity’s workforce, that create, receive, maintain, or transmit 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 sanctions 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 program 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 and entities. Recently, states have enacted or are considering legislation intended to make drug prices more transparent and deter significant price increases that impose reporting requirements on biopharmaceutical companies. These laws may affect our future sales, marketing, and other promotional activities by imposing administrative and compliance burdens. Such laws also typically impose significant civil monetary penalties for each instance of reporting noncompliance that can quickly aggregate into the tens of millions of dollars.

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 significant civil monetary penalties, damages, criminal fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, corporate integrity agreements, suspension and debarment from government procurement and non-procurement programs, 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, imposes certain recordkeeping requirements and 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 healthcare 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. While this rule now has been rescinded, government negotiation of certain Medicare drug pricing continues to be the focus of recent proposed legislation. The Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. Failure of the Joint Select Committee on Deficit Reduction to reach required deficit reduction goals triggered the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year. While President Biden previously signed legislation to eliminate this reduction through the end of 2021, recent legislation will restart the reductions, which will thereafter remain in effect through 2031 unless additional congressional action is taken. 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 U.S. has increased and will continue to increase the pressure on drug pricing. Decisions regarding whether to cover any of our products, the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. Further, no uniform policy for coverage and reimbursement exists in the U.S., and coverage and reimbursement can differ significantly from payor to payor. 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 healthcare 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 U.S.. 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 Trial Regulation EU 536/2014 (“CTR”), which replaced the Clinical Trials Directive 2001/20/EC, as amended (“CTD”), on January 31, 2022, provides a system for the approval of clinical trials in the European Union. The CTR is directly applicable in all member states without the need for national implementation. Whilst, for trials conducted in only one country, approval has to be obtained from the competent national authority of an EU member state in which the clinical trial is to be conducted before cross-border trials within the EU, it is possible 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” (Directive 2001/18/EC). As a consequence, in some EU member states the GMO application must be approved before the CTA is submitted, in some after approval of the CTA, and in some, in 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. Under the CTR, 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.

Under the CTR, the introduction of a new databased called the Clinical Trial Information System (“CTIS”), requires sponsors to upload and submit all data, including initial clinical trial application data and documentation, to the CTIS, with such data being publicly available, with few exceptions. This means data transparency throughout the development process with the onus on sponsors to protect patient confidentiality at the point of submission.

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 27 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 nonclinical 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 dezaparvec.

Orphan Drug Regulation

We have been granted orphan drug exclusivity for etranacogene dezaparvec 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, 2022, we had a total of 501 employees, 290 of whom are based in The Netherlands, 199 in the U.S., and 12 in other European countries. As of December 31, 2022, 110 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 agreements 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.

Our people are a critical component in our continued success. We strive to maximize the potential of our human capital resources by creating a respectful, rewarding and inclusive work environment that enables our employees to further our values. 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. In 2021 and 2022, we initiated activities to coordinate our various ongoing activities and initiatives within an environmental, social and governance (“ESG”) framework.

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 25, Amsterdam 1105 BP, the Netherlands and its telephone number is +31 20 240 6000.

[Table of Contents](#)

Our website address is www.unique.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 (the "Board") 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 Current Covid Pandemic

Our business, operations, human resources and supply chain have been, and may continue to be, materially and adversely affected by the ongoing Covid pandemic.

On March 11, 2020, the World Health Organization (“WHO”) declared the ongoing outbreak of coronavirus disease (“Covid”) a pandemic. The Covid pandemic is affecting the U.S. and global economies and has affected and may continue to affect our operations and those of third parties on which we rely. The Covid 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 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.

Global supply chains have been disrupted, causing shortages, which could further impact our clinical trials. This disruption of our employees, distributors and suppliers has historically impacted and may continue to impact our future operating results. Additionally, to the extent that inspections of facilities by governmental authorities are required, the review of our marketing applications or supplements may further be delayed as regulatory authorities, such as FDA, have significantly limited facility inspections during the pandemic.

We may also be subject to further laws, regulations, guidelines, executive orders and other requirements at the federal, state and local levels related to the pandemic, which we may be required to undertake or that we choose to undertake. Any such requirements or guidelines that we adopt could have a material impact on our business operations.

Risks Related to the Development of Our Product Candidates

Our product candidates in development have not yet been approved for commercial sale and they might never receive regulatory approval or become commercially viable. We have never generated any significant revenue from product sales and may never be profitable.

Our pipeline consists of product candidates in research or development that have not been approved for commercial sale. We have not generated any revenues from the sale of products or manufacturing of a product for a third party and do not expect to generate any such revenue until this year, at the earliest. Our product candidates including 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 have encountered and may encounter future 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, we experienced an immaterial but unexpected delay when our clinical trials of HEMGENIX™ were placed on clinical hold by the FDA from December 2020 to April 2021, following a preliminary diagnosis of hepatocellular carcinoma in one patient. Similarly, we experienced an unexpected delay in the enrollment of our Phase Ib/II clinical trial for Huntington’s disease between July and October 2022 as a result of our voluntary postponement and comprehensive safety investigation into suspected unexpected serious adverse reactions in three patients.

We cannot guarantee that any preclinical tests or clinical trials 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;
- changes in standards of care which may necessitate the modification of our clinical trials or the conduct of new 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;
- recommendations from DSMBs to discontinue, pause, or modify the trial;
- 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;
- 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 emergence 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 (such as the EU Clinical Trials Regulation), 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 U.S. 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 or 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.

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.

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. Moreover, in the U.S., FDA expects that sponsors with products under these programs will be prepared for a more rapid pace of development, including with respect to manufacturing or any combination medical devices, such as companion diagnostics. If we are unable to meet these expectations, we may not be able to fully avail ourselves of certain advantages of these programs.

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), etranacogene dezaparvovec, and AMT-130. However, 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 or otherwise being dependent upon additional regulatory approvals. 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.

It is possible that our product candidates would be 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, EU member state, and other regulatory bodies to ensure compliance with current cGMP requirements. 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, EU member state, 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, EMA, EU and other regulatory authority 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 of our manufacturing processes, that may result in delays in regulatory approvals, inability to produce sufficient amounts of commercial product, or otherwise adversely affect our ability to manufacture sufficient amounts 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, war or cases of force majeure and acts of god (including the effects of the Covid 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 U.S. 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 and methods, or develop new processes and methods to meet our product supply needs and obligations.

The manufacture of our AAV gene therapies 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 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 gene therapy product candidates we will need to complete the validation of our manufacturing processes and methods, and we may need to develop and validate new or larger scale manufacturing processes and methods. If we are unable to consistently manufacture our gene therapy product candidates or any approved products in accordance with our pre-specified quality parameters and applicable regulatory standards, it could adversely impact our ability to validate our manufacturing processes and methods, to meet our production needs, to file a 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.

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 U.S., 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 U.S. 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 may also be delayed in completing their review of any marketing applications submitted by us or our partners. 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.

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 U.S., 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 U.S. or EU, 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 U.S., there have been a number of recent changes relating to gene therapy development. By example, FDA issued a number of new guidance documents, and continues to issue guidance documents, on human gene therapy development, one of which was specific to human gene therapy for hemophilia, one that was specific to neurodegenerative diseases, 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 U.S. 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 U.S. 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 U.S., 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 U.S. 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. Moreover, in the U.S. the exact scope of orphan exclusivity is currently uncertain and evolving due to a recent court decision.

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 U.S., whether two gene therapies are considered to be the same for the purpose of determining clinical superiority was recently updated via a final guidance document specific to gene therapies, and depends on a number of factors, including the expressed transgene, the vector, and other product or product candidate features. Depending on the products, whether two products are ultimately considered to be the same may be determined by FDA on a case-by-case basis, making it difficult to make predictions regarding when FDA might be able to make an approval of a product effective and whether periods of exclusivity will effectively block competitors seeking to market products that are the same or similar to ours for the same intended use. 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 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 U.S., this could mean that a competing biosimilar product may be able to submit an application to the FDA and obtain approval either as a biosimilar to one of our products or even as an interchangeable product. 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 judgment. 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 U.S. period of exclusivity to a shorter timeframe. Future proposed budgets, international trade agreements and other arrangements or proposals may affect periods of exclusivity.

If any of our product candidates receive regulatory approval, we and/or our partners will be subject to extensive regulatory requirements. Failure to fulfill and comply with the applicable regulatory requirements could result in regulatory enforcement actions that would be detrimental to our business.

Following any regulatory approval, the FDA and the EMA may impose certain post-approval requirements related to a product. Specifically, any approved products will be subject to continuing and comprehensive regulation concerning the product's design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution. Regulatory authorities may also require post-marketing testing, known as Phase 4 testing, a risk evaluation and mitigation strategy, and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. Failure to comply with any of these requirements could result in regulatory, administrative, or other enforcement action, that would be detrimental to our business.

For instance, the FDA and other government agencies closely regulate the post-approval marketing and promotion of approved products, including off-label promotion, industry-sponsored scientific and educational activities, and the Internet and social media. Approved products may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Failure to comply with regulatory promotional standards could result in actions being brought against us by these agencies.

Moreover, if a company obtains FDA approval for a product via the accelerated approval pathway, the company would be required to conduct a post-marketing confirmatory trial to verify and describe the clinical benefit in support of full approval. FDA can require that this confirmatory trial be commenced prior to FDA granting a product accelerated approval. An unsuccessful post-marketing study or failure to complete such a study could result in the expedited withdrawal of the FDA's marketing approval for a product using a statutorily defined streamlined process.

Changes to some of the conditions established in an approved application, including changes in labeling, indications, manufacturing processes or facilities, may require a submission to and approval by the FDA or the EMA, as applicable, before the change can be implemented. A New Drug Application (“NDA”)/BLA or MAA supplement for a new indication typically requires clinical data similar to that in the original application. The applicable regulatory authorities would review such supplement using similar procedures and actions as in reviewing NDAs/BLAs and MAAs.

Adverse event reporting and submission of periodic reports is required following marketing approval. Regulatory authorities may withdraw product approvals or request product recalls, as well as impose other enforcement 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.

In addition, the manufacture, testing, packaging, labeling, and distribution of products after approval will need to continue to conform to cGMPs. Drug and biological product manufacturers and certain of their subcontractors are subject to periodic unannounced inspections by the FDA or the EMA for compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs. In addition, prescription drug manufacturers in the U.S. must comply with applicable provisions of the Drug Supply Chain Security Act and provide and receive product tracing information, maintain appropriate licenses, ensure they only work with other properly licensed entities and have procedures in place to identify and properly handle suspect and illegitimate products.

Where we partner with third parties for the development, approval, and marketing of a product, such third parties will be subject to the same regulatory obligations as we will. However, as we will not control the actions of the applicable third parties, we will be reliant on them to meet their contractual and regulatory obligations. Accordingly, actions taken by any of our partners could materially and adversely impact our business.

Risks Related to Commercialization

If we, or our commercial partner, 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 revenues from HEMGENIX™ or any other product will depend on the successful development and eventual commercialization of our product candidates. The success of HEMGENIX™ or other product candidates will depend on many factors, including:

- successful execution of our contractual relationship with CSL Behring for the commercialization of HEMGENIX™;
- 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 HEMGENIX™ and other products according to required quality specifications;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivities for our product candidates;
- 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 for HEMGENIX™ and other products;
- any price concessions, rebates, or discounts we may need to provide;
- complying with any applicable post-approval commitments and 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.

CSL Behring may not receive a conditional marketing authorization based on an accelerated assessment by the EMA for AMT-061 product candidate to facilitate a first commercial sale in the European Union prior to July 2, 2023, and we, thus, may not receive the \$75.0 million first commercial sale milestone in any of the five contractually defined European countries prior to July 2, 2023 under the CSL Behring Agreement.

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.

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 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 U.S., 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. Public and medical community adoption of any of our gene therapies will also depend on factors including the ease of administration in comparison to other therapeutics. By example, the need for complex surgeries for the administration of a product candidate may impact the acceptance of a product.

In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product and product candidates, prescribing treatments that involve the use of our product and product candidates, 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, or our commercial partner, obtain approval to commercialize any of our product candidates outside of the U.S., 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 U. S., 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 U.S.;
- 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 U.S.;
- 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.

In February 2022, armed conflict escalated between Russia and Ukraine. The sanctions announced by the U.S. and other countries following Russia's invasion of Ukraine against Russia to date include restrictions on selling or importing goods, services or technology in or from affected regions and travel bans and asset freezes impacting connected individuals and political, military, business and financial organizations in Russia. The U.S. and other countries could impose wider sanctions and take other actions should the conflict further escalate. It is not possible to predict the broader consequences of this conflict, which could include further sanctions, embargoes, regional instability, geopolitical shifts and adverse effects on macroeconomic conditions, currency exchange rates and financial markets, all of which could impact our business, financial condition and results of operations.

We may be adversely affected by the effects of inflation.

Inflation has the potential to adversely affect our liquidity, business, financial condition and results of operations by increasing our overall cost structure. The existence of inflation in the economy has resulted in, and may continue to result in, higher interest rates and capital costs, shipping costs, supply shortages, increased costs of labor, weakening exchange rates and other similar effects. As a result of inflation, we have experienced and may continue to experience, cost increases. Although we may take measures to mitigate the impact of this inflation, if these measures are not effective our business, financial condition, results of operations and liquidity could be materially adversely affected. Even if such measures are effective, there could be a difference between the timing of when these beneficial actions impact our results of operations and when the cost inflation is incurred.

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 face worldwide competition from larger pharmaceutical companies, specialty pharmaceutical companies and biotechnology firms, universities and other research institutions and government agencies that are developing and commercializing pharmaceutical products. Our key competitors focused on developing therapies in various indications, include among others, Pfizer, Freeline Therapeutics, Intellia Therapeutics, Sangamo Biosciences, Voyager Therapeutics, Passage Bio, Roche, PTC Therapeutics, Prilenia Therapeutics, CombiGene, Caritas Therapeutics, Alnylam, Wave Life Sciences, Bayer AG, Amicus Therapeutics and 4D Molecular Therapeutics.

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 U.S., 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. Patents we own currently are and may become subject to future patent opposition or similar proceedings. For example, we are currently defending a patent case in each of Canada, the United Kingdom, and the US and have filed Notices of Appeal at the CAFC contesting three FWDs. These oppositions and future patent oppositions 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 U.S.. 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 U.S. 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 U.S. 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 U.S. 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 U.S. 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 U.S. 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 Business Development

Our business development strategy may not produce the cash flows expected or could result in additional costs and challenges.

Any business development transaction could expose us to unknown liabilities and risks, and we may incur additional costs and expenses necessary to address an acquired company's failure to comply with laws and governmental rules and regulations. We could incur additional costs related to resources to align our business practices and operations. Moreover, we cannot assure that the anticipated benefits of any acquisition would be realized in a timely manner, if at all.

Risks Related to Pricing and Reimbursement

We, and our commercial partner, face uncertainty related to insurance coverage of, and pricing and reimbursement for HEMGENIX™ and other 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 U.S. 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 ("MFN") 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. While this rule now has been rescinded, government negotiation of certain Medicare drug pricing continues to be the focus of recent proposed legislation.

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 HEMGENIX™ and other 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 had a loss in the current year, gain in the year ended December 31, 2021, but incurred significant losses in previous years and expect to incur losses over the next several years and may never achieve or maintain profitability.

We had net loss of \$126.8 million in the year ended December 31, 2022, incurred a gain of \$329.6 million in 2021 and incurred a net loss of \$125.0 million in 2020. As of December 31, 2022, we had an accumulated deficit of \$581.9 million. In the past, 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 expect to finance our operations in 2023 primarily from our existing cash resources including payments we collected and expect to collect in relation to the CSL Behring Agreement. 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.

We anticipate that our expenses will increase for the foreseeable future and will include costs related to:

- advancing AMT-130 for our Huntington's disease gene therapy program into phase III clinical study;
- advancing our gene therapy programs for rTLE, SOD1-ALS and Fabry disease into Phase I/II clinical studies;
- potentially acquiring or in-licensing rights to new therapeutic targets, product candidates and technologies;
- making potential future milestone payments related to the acquisition of Corlieve, if any;
- advancing preclinical research and development for gene therapy product candidates targeting other diseases; and
- continuing to invest in expanding, developing and optimizing our manufacturing capabilities and other enabling technologies, such as next-generation viral vectors, promoters and re-dosing.

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 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 2021 Restated Facility with Hercules Capital Inc. (“Hercules”) that we entered into on December 15, 2021 when the Company and Hercules amended and restated the 2021 Amended Facility (the “2021 Restated Facility”) 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, 2022, we had \$100.0 million of outstanding principal of borrowings under the 2021 Restated Facility, which we are required to repay in full in December 2025. 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 2021 Restated 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 employees, customers and third-parties is subject to applicable laws and regulations, the non-compliance of any of which could have a material adverse effect on our business, financial condition, and results of operations.

Healthcare providers, physicians, other practitioners, 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 U.S. and international 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 from participation in government funded healthcare programs and the curtailment or restructuring of our operations.

Additionally, we are subject to various labor and employment laws and regulations. These laws and regulations relate to matters such as employment discrimination, wage and hour laws, requirements to provide meal and rest periods or other benefits, family leave mandates, employee and independent contractor classification rules, requirements regarding working conditions and accommodations to certain employees, citizenship or work authorization and related requirements, insurance and workers' compensation rules, healthcare laws, scheduling notification requirements and anti-discrimination and anti-harassment laws. Complying with these laws and regulations, including ongoing changes thereto, subjects us to substantial expense and non-compliance could expose us to significant liabilities. In particular, we are subject to allegations of Sarbanes-Oxley whistleblower retaliation and employment discrimination and retaliation, and we may in the future be subject to additional claims of non-compliance of similar or other Laws and regulations.

The costs associated with a violation of any of the foregoing 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 10,000,000 per occurrence. 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 U.S., 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, Congress subsequently has extended the period over which these reductions are in effect. While President Biden previously signed legislation temporarily to eliminate this reduction through the end of 2021, recent legislation will restart the reductions, which will thereafter remain in effect through 2031 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 pricing and the reimbursement our customers may receive for our products, and increased manufacturer rebates. 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 might increase our vulnerability to the above risk.

While we have experienced and addressed system failures, cyber-attacks, and security breaches in the past, 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. 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.

Climate change, environmental, social and governance and sustainability initiatives may result in regulatory or structural industry changes that could require significant operational changes and expenditures, reduce demand for the Company's products and adversely affect our business, financial condition, and results of operations.

Greenhouse gases may have an adverse effect on global temperatures, weather patterns, and the frequency and severity of extreme weather and natural disasters. Such events could have a negative effect on our business. Concern over climate change may result in new or additional legislative and regulatory requirements to reduce or mitigate the effects of climate change on the environment, which could result in future tax, transportation cost, and utility increases. Moreover, natural disasters and extreme weather conditions may impact the productivity of our facilities, the operation of our supply chain, or consumer buying patterns. Any of these risks could have a material adverse effect on our business.

Climate change, environmental, social and governance and sustainability initiatives may result in regulatory or structural industry changes that could require significant operational changes and expenditures, reduce demand for the Company's products and adversely affect our business, financial condition, and results of operations.

Climate change, environmental, social and governance and sustainability are a growing global movement. Continuing political and social attention to these issues has resulted in both existing and pending international agreements and national, regional and local legislation, regulatory measures, reporting obligations and policy changes. Also, there is increasing societal pressure in some of the areas where we operate, to limit greenhouse gas emissions as well as other global initiatives. These agreements and measures, including the Paris Climate Accord, may require, or could result in future legislation, regulatory measures or policy changes that would require operational changes, taxes, or purchases of emission credits to reduce emission of greenhouse gases from our operations, which may result in substantial capital expenditures.

Furthermore, increasing attention to climate change, ESG and sustainability has resulted in governmental investigations, and public and private litigation, which could increase our costs or otherwise adversely affect our business or results of operations. In addition, organizations that provide information to investors on corporate governance and related matters have developed ratings processes for evaluating companies on their approach to ESG matters. Such ratings are used by some investors to inform their investment and voting decisions. Unfavorable ESG ratings may lead to increased negative investor sentiment toward us, which could have a negative impact on the price of our securities and our access to and costs of capital.

Any or all of these ESG and sustainability initiatives may result in significant operational changes and expenditures, reduced demand for our products, cause us reputational harm, and could materially adversely affect our business, financial condition, and results of operations.

Risks Related to Employee Matters and Managing Growth

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

Our future growth and success will depend in large part on our continued ability to attract, retain, manage and motivate our employees. The loss of the services of any member of our senior management or the inability to hire or retain experienced management personnel could adversely affect our ability to execute our business plan and harm our operating results. 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.

The competition for qualified personnel in the pharmaceutical field is intense, and there is a limited pool of qualified potential employees to recruit. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business or to recruit suitable replacement personnel. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our business may be harmed and our growth strategy may be limited.

Additionally, we are reliant on our employees, contractors, consultants, vendors and other parties with whom we have relationships to behave ethically and within the requirements of the law. The failure of any employee or other such third parties to act within the bounds of the applicable laws, regulations, agreements, codes and other requirements, or any misconduct or illegal actions or omissions by such persons, could materially damage our business.

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 23, 2023, 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 23, 2022, was \$20.06 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 EU, the U.S., 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 39.4% of our issued shares (including such shares to be issued in relation to exercisable options to purchase ordinary shares) as at December 31, 2022. 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 and 2022 but not for 2017 through 2021. A corporation organized outside the U.S. 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 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 U.S.. As a result, it may not be possible for shareholders to effect service of process within the U.S. 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 U.S.. 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 U.S. 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 U.S., 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 U.S. 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 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 foot GMP qualified manufacturing facility that we lease in Lexington, Massachusetts, U.S. 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.

In December 2021, we entered into a new lease for an additional laboratory and office facility in Lexington, Massachusetts, U.S. of approximately 13,501 square feet of space. The lease commenced in May 2022, is set for seven years and is non-cancellable. The lease is renewable for one five-year term.

In February 2022, we also entered into a new lease for a multi user office-building in Lexington, Massachusetts, U.S. of approximately 12,716 square feet. The lease commenced in November 2022 and is set for a non-cancellable period of seven years and four months. The lease is renewable for one five-year term.

Amsterdam / The Netherlands

In 2016, we entered into leases for a total of approximately 111,000 square feet multi-tenant facility in Amsterdam. The lease for parts of 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.

In May 2021, we entered into a sublease agreement to let an additional approximately 1,080 square meters of office space in the multi-tenant facility. The lease expires in October 2028 and includes an option to break the lease on October 31, 2023.

Basel / Switzerland

In May 2022, we entered into a sublease agreement to let approximately 81 square meters comprising of four co-workers spaces in a multi user office-building to accommodate our employees in Basel, Switzerland. We subleased an additional room beginning in December 2022 for a total of approximately 100 square meters. The lease expires on June 30, 2032.

We believe that our 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.

None.

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 of 1933, as amended (the “Securities Act”).

Issuer Share Repurchases

We did not make any purchases of our ordinary shares during the period covered by this Annual Report on Form 10-K.

Holdings

As of February 23, 2023, 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 close on December 31, 2017 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, except to the extent incorporated by reference, is not to be incorporated by reference into any of our filings under the Securities Act, or the U.S. Securities Exchange Act of 1934, as amended (the “Exchange Act”), whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.



Item 6. Reserved

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 U.S. (“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 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. 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 and seek to deliver to patients suffering from rare and other devastating diseases single treatments with potentially curative results. We are advancing a pipeline of innovative gene therapies, including our clinical candidates for the treatment of Huntington’s disease and ALS, as well as preclinical product candidates including candidates for the treatment of rTLE and Fabry disease. In November 2022 and February 2023, our internally-developed HEMGENIX[®], a gene therapy for the treatment of hemophilia B, was approved for commercialization by the FDA and the EMA, respectively. In June 2020, we agreed to license HEMGENIX[®] to CSL Behring, which is now responsible for commercialization of HEMGENIX[®]. We are manufacturing HEMGENIX[®] for CSL Behring and are entitled to specific milestone payments and royalties on net sales. 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 collaboration

In June 2020 we entered into the CSL Behring Agreement pursuant to which CSL Behring received exclusive global rights to the Product. The transaction became fully effective in May 2021.

In March and April 2022, CSL Behring submitted marketing applications for HEMGENIX[®] in the U.S. and the EU. In March and April 2022, we received the \$55.0 million owed to us by CSL Behring related to submission of these marketing applications.

In November 2022, the FDA approved the marketing application for the U.S. and in February 2023 the EMA approved the marketing application for the EU. We are eligible to receive a \$100.0 million payment from CSL Behring following the first sale of the Product in the U.S. We are also eligible to receive a \$75.0 million payment from CSL Behring following the first sale of the Product in any of five major European countries, namely France, Germany, Italy, Spain, and the United Kingdom, provided the first sale occurs prior to July 2, 2023. We recorded the \$100.0 million payment associated with the first sale in the U.S. as license revenue in the year ended December 31, 2022 as we expect this event to occur in 2023. We did not record license revenue related to a \$75.0 million payment in the year ended December 31, 2022 as the accomplishment of this milestone prior to July 2, 2023 is contingent on factors outside of our control.

Concurrently with the execution of the CSL Behring Agreement, we and CSL Behring also 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 commensurate with the stand-alone selling price (“SSP”) until such time that these capabilities are transferred to CSL Behring or its designated contract manufacturing organization. We completed the validation of the current manufacturing process and in July 2022, following a comprehensive multi-day facility inspection, the EMA notified us that GMP certification can be issued for our Lexington, Massachusetts-based manufacturing site to produce commercial supply of HEMGENIX[®]. In August 2022, we completed the FDA pre-license inspection of the Lexington facility. On September 6, 2022 CSL Behring notified us of its intent to transfer manufacturing technology related to the Product in the coming years to a third-party contract manufacturer designated by CSL Behring. CSL Behring also informed us of its intent to retain us as a source for manufacturing after the completion of the technology transfer.

In August 2022, the GMP certification for the Amsterdam facility was amended to include release testing of the Product in the European Union following inspection by the IGJ.

We recorded \$1.7 million in revenue related to manufacturing the Product in the year ended December 31, 2022.

Huntington’s disease program (AMT-130)

On March 21, 2022, we announced that we have completed the enrollment of all 26 patients in the first two cohorts of our Phase I/II clinical trial of AMT-130 taking place in the U.S. The low-dose cohort includes 10 patients, of which six patients received treatment with AMT-130 and four patients received imitation surgery. The higher-dose cohort includes 16 patients, of which 10 patients received treatment with AMT-130 and six patients received imitation surgery. In July 2022 we crossed over one of these six patients and treated the patient with the lower dose of AMT-130.

On June 23, 2022, we announced encouraging safety and biomarker data from the 10 patients enrolled in the low-dose U.S. cohort. AMT-130 was generally well-tolerated with no serious adverse events related to AMT-130 reported in the treated patients. In the four treated patients with evaluable data, mean levels of CSF mHTT declined at all timepoints compared to baseline and decreased by 53.8% at 12 months of follow-up. In the six treated patients, measurements of CSF NfL initially increased as expected following the AMT-130 surgical procedure and declined thereafter, nearing baseline at 12 months of follow-up.

In August 2022, we announced a voluntary postponement of AMT-130 higher-dose procedures due to SUSARs reported in three of the 14 patients that were treated with the higher dose of AMT-130. In October 2022, after completing a comprehensive safety investigation, the DSMB recommended resuming treatment at the higher dose of AMT-130 for the remaining five European patients and any patients in the U.S. trial eligible to cross over from the control arm to the treatment. All three patients have experienced full resolution of the reported SUSARs.

Acquisition of Corlieve Therapeutics

On June 21, 2021, we entered into a Sale and Purchase Agreement (“SPA”) to acquire all outstanding ordinary shares of Corlieve SAS (“Corlieve”), a privately held French gene therapy company (the “Corlieve Transaction”). Upon the closing of the Corlieve Transaction on July 30, 2021 (the “Acquisition Date”), we acquired 97.7% of the outstanding ordinary shares of Corlieve in return for EUR 44.9 million (\$53.3 million as of the Acquisition Date). We paid EUR 1.8 million (\$1.9 million) to acquire the remaining shares of Corlieve in 2022. We financed the Corlieve Transaction from cash on hand.

In addition to the payments to acquire 100% of the outstanding ordinary shares, Corlieve’s former and remaining shareholders are eligible to receive up to EUR 40.0 million (or \$42.8 million as of December 31, 2022) upon the achievement of development milestones through Phase I/II and EUR 160.0 million (or \$171.3 million as of December 31, 2022) upon the achievement of milestones associated with Phase III development and obtaining approval to commercialize AMT-260 in the U.S. and the EU. We expect these obligations will become payable between 2023 and 2031. If and when due, we may elect to pay up to 25% of such milestone payments through the issuance of our ordinary shares.

Termination of Bristol-Myers Squibb Agreement

In May 2015 we and BMS entered the BMS CLA. The initial four-year research term under the collaboration terminated in May 2019. On December 1, 2020, we and BMS amended the BMS CLA. As a result of the Amended BMS CLA, we recognized the remaining balance of license revenue of \$27.8 million not previously recognized during the year ended December 31, 2020. The Amended BMS CLA did not extend the initial research term. For a period of one-year from the effective date of the Amended BMS CLA, BMS was able to replace up to two of the four active collaboration targets with two new targets in the field of cardiovascular disease. BMS did not replace any of the active collaboration targets. On December 17, 2020, BMS designated one of the four collaboration targets as a candidate to advance into Investigational New Drug-enabling studies (“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 year ended December 31, 2020.

On November 21, 2022 we received the Termination Notice whereby the Amended BMS CLA terminated on February 21, 2023.

The Amended BMS CLA terminated two warrants that, when in effect, provided BMS the right to increase its ownership in the Company up to 19.9% upon the exercise of both warrants, with the exercise of such warrants being conditioned on the designation of a seventh, and a tenth Collaboration Target, respectively. In the Amended BMS CLA, 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) would 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 would 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 would be an amount equal to one percent of such net proceeds. We had not consummated any change of control transaction as of the Termination Notice and as of December 31, 2022, assessed the probability as of the Termination Date and released the liability related to the change of control payment to other income during the year ended December 31, 2022.

The Termination Notice did not change any of the provisions of the Investor Agreement with BMS that we entered into in 2015, but various provisions of the Investor Agreement have been terminated. We have granted BMS certain registration rights that allow BMS to require us to register our securities beneficially held by BMS under the Securities Act. BMS may make up to two such demands for us to register the shares, subject to customary limitations. 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, 2022 BMS held 5.08%). 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 or the closing of a transaction that provides BMS exclusive and absolute discretion to vote our shares it beneficially holds.

Investment in debt securities

In December 2022, we invested \$100.0 million and EUR 80.0 million (or total of \$183.9 million as of investment date) of our cash on hand into short-term and long-term euro and dollar denominated sovereign bonds. The bonds have remaining maturities ranging from two to 14 months. We classify these bonds as held-to-maturity. We made no such investments in 2021 and 2020.

Covid pandemic

The coronavirus disease (“Covid”) caused by the severe acute respiratory syndrome coronavirus 2 (“Sars-CoV 2 virus”) was characterized as a pandemic by the WHO on March 11, 2020. Since then, various variants of the Sars-CoV 2 virus causing Covid have been identified.

The broader implications of Covid, including the implications from the various variants, on our results of operations and overall financial performance remain uncertain. We have experienced and continue to experience increased lead times in the delivery of equipment and disposables that we use to manufacture materials for our various programs. Currently, these have not materially impacted our development timelines and we continue to adapt to the current environment to minimize the effect to our business. However, we may experience more pronounced disruptions in our operations in the future.

Russian-Ukrainian war

Our business is not directly impacted by the war as we do not operate in either Russia or the Ukraine. However, the war might potentially amplify the disruptive impact of the Covid pandemic.

Financial Highlights

Key components of our results of operations include the following:

	Year ended December 31,		
	2022	2021	2020
		(in thousands)	
Total revenues	\$ 106,483	\$ 524,002	\$ 37,514
Cost of revenues	(3,343)	(24,976)	—
Research and development expenses	(197,591)	(143,548)	(122,400)
Selling, general and administrative expenses	(55,059)	(56,290)	(42,580)
Net (loss) / income	(126,789)	329,589	(125,024)

As of December 31, 2022, we had \$392.8 million in cash and cash equivalents and investment securities (December 31, 2021: \$556.3 million cash and cash equivalents). We had a net loss of \$126.8 million in 2022, and net income of \$329.6 million in 2021 and a net loss of \$125.0 million in 2020. As of December 31, 2022, we had an accumulated deficit of \$581.9 million (December 31, 2021: \$455.1 million).

We anticipate that our expenses will increase for the foreseeable future and will include costs related to:

- advancing AMT-130 for our Huntington’s disease gene therapy program into phase III clinical study;
- advancing our gene therapy programs rTLE, SOD1-ALS and Fabry disease into Phase I/II clinical studies;
- potentially acquiring or in-licensing rights to new therapeutic targets, product candidates and technologies;
- making potential future milestone payments related to the acquisition of Corlieve, if any;

- advancing preclinical research and development for gene therapy product candidates targeting other diseases; and
- continuing to invest in expanding, developing and optimizing our manufacturing capabilities and other enabling technologies, such as next-generation viral vectors, promoters and re-dosing.

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 loss/income and affect the reported amounts of certain assets, liabilities, revenue and expenses, and related disclosures. On an ongoing basis, we evaluate our assumptions, estimates and judgments, including those related to what we believe to be our critical accounting policies. Refer to Note 2 “*Summary of significant accounting policies*” for a summary of our significant accounting policies.

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, judgments or estimates. We also discuss our critical accounting estimates with the Audit Committee of our Board of Directors.

We consider the following to be our critical accounting estimates:

- Recognition of revenue including the CSL Behring milestones in relation to the CSL Behring Agreement;
- Contingent consideration recorded in relation to the Corlieve business combination; and
- Valuation allowance related to Dutch and U.S. deferred tax assets.

Revenue recognition related to CSL Behring milestones

On the Signing Date we entered into the CSL Behring Agreement. The transaction became effective on Closing.

As of Closing, we identified two material performance obligations related to the CSL Behring Agreement:

- (i) Sale of the exclusive global rights to the Product (“License Sale”); and
- (ii) Generate information to support the regulatory approval of the current and next generation manufacturing process of Product and to provide any such information generated to CSL Behring (“Manufacturing Development”).

We determined that the fixed upfront payment of \$450.0 million and the \$12.4 million that we received in relation to the certain reimbursable activities to fulfill the transfer of global rights (“Additional Covenants”) in the year ended December 31, 2021 should be allocated to the License Sale. In addition, we concluded that \$255.0 million of variable milestone payments, sales milestone payments and royalties should be allocated to the License Sale performance obligation as well. We determined that the License Sale was completed on May 6, 2021, when we transferred the license and CSL Behring assumed full responsibility for the development and commercialization of the Product. Upon the Closing, we evaluated the amounts of potential payments and the likelihood that the payments will be received. We utilized the most likely amount method to estimate the variable consideration to be included in the transaction price. Since we cannot control the achievement of regulatory and first commercial sales milestones, we concluded that all potential payments were constrained as of Closing. We determined that we would recognize revenue related to these payments, only to the extent that it becomes probable that no significant reversal of recognized cumulative revenue will occur thereafter. We will include payments related to sales milestones in the transaction price when their achievement becomes probable, and we will include royalties on the sale of Product once these have been earned.

In March and April 2022, we collected the \$55.0 million of variable milestone payments related to the submissions of a BLA and MAA which we had recorded as license revenue in the year ended December 31, 2021. During the year ended December 31, 2022, we recorded \$100.0 million of variable milestone revenue related to a first sale of HEMGENIX™ in the U.S. as we consider this to be probable following the November 2022 FDA approval of HEMGENIX™. Despite the approval of the MAA for HEMGENIX™ by the EMA in February 2023, we did not record the \$75.0 million variable milestone payment related to a first sale of HEMGENIX™ in the one of five major European countries, namely France, Germany, Italy, Spain, and the United Kingdom, as license revenue in the year ended December 31, 2022 as the payment is contingent on the milestone being achieved prior to July 2, 2023, which is contingent on factors outside our control.

Contingent consideration

On the Acquisition Date of Corlieve we recorded contingent consideration related to amounts potentially payable to Corlieve's former shareholders. The amounts payable in accordance with the SPA are contingent upon realization of certain milestones associated with the TLE research program. Contingent consideration was measured at fair value at the Acquisition Date with changes in fair value recognized in the consolidated statements of operations in research and development expenses.

Changes in contingent consideration can result from changes in the assumed achievement and timing of estimated milestones and the discount rate used to estimate the fair value of the liability:

- We had used discount rates ranging from 10.9% to 11.9% to calculate the contingent consideration as of December 31, 2021. As of December 31, 2022 we increased the interest rates to a range of 14.0% to 14.4% to reflect increases in market interest rates. An increase in the discount rate reduces the fair value of the contingent consideration liability whereas a decrease in the discount rate increases the fair market value of the contingent consideration liability.
- As of December 31, 2021, we had estimated that AMT-260 would advance into the clinical development by early 2024, and as of December 31, 2022, we revised that estimate to late 2023. An achievement of a milestone at a later than currently expected date reduces the fair value of the contingent consideration liability whereas an achievement at an earlier than currently expected date increases the fair value of the contingent consideration liability.
- We initially recorded the contingent consideration liability on the Acquisition Date assuming a 40% probability of advancing the TLE research program into clinical development. We developed this estimate using data from an external study regarding the average likelihood of advancing into clinical development at a certain stage or preclinical development. For the year ended December 31, 2021, we had increased the probability to 55.0% following the designation of a lead candidate by us in late October 2021. During the year ended December 31, 2022 we increased the probability to 66.0% following the commencement of toxicology studies for the TLE program. The increase in probabilities resulted in a \$4.4 million expense in the year ended December 31, 2022 and a \$5.8 million expense in the year ended December 31, 2021.

The fair value of the contingent consideration liability as of December 31, 2022 was \$35.3 million and as of December 31, 2021 was \$29.5 million. The increase was primarily driven by an increase in the probability of the TLE program advancing into clinical development. If as of December 31, 2022 we had assumed TLE was certain (i.e. 100% probability) to advance into clinical development, then the fair value of the contingent consideration liability would have increased from \$35.3 million to \$48.8 million. If as of December 31, 2022 we had assumed that we would discontinue development of the TLE program, then we could have released the contingent consideration liability to income.

Valuation allowance related to Dutch and U.S. deferred tax assets

We are subject to corporate taxes in the Netherlands. We have been incurring net operating losses in accordance with the corporate tax laws in almost all years since we founded our business.

As of December 31, 2022, the total amount of net operating losses carried forward under the Dutch tax regime was \$264.0 million (December 31, 2021: \$228.5 million). We have historically recorded a full valuation allowance. We evaluate all positive and negative evidence including future income from the CSL Behring Agreement in assessing the need for such a full valuation allowance. We concluded that as of December 31, 2022 it is more likely than not that the remaining deferred tax assets will not be realized. If we would have released the full valuation allowance as of December 31, 2022, then we would have recorded up to \$74.5 million of deferred tax income during the year ended December 31, 2022.

We are also subject to corporate taxes in the U.S.. While our operations in the U.S. had initially been incurring net operating tax losses, our subsidiary in the U.S. generated taxable income in the past few years starting with 2018. Based on the design of our worldwide operations, we determined as of December 31, 2020 that we expect to continue to generate taxable income in the U.S. during the foreseeable future and therefore determined that it had become more likely than not that our U.S. deferred tax assets will be realized. Accordingly, 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 U.S.. We generated taxable income in the U.S. during the years ended December 31, 2021 and December 31, 2022 and therefore continue to expect that it is more likely than not that our U.S. deferred tax assets will be realized. We would be required to record deferred tax expense to recognize a valuation allowance on a portion of or possibly even our full U.S. deferred tax asset of \$21.1 million as of December 31, 2022, if we would expect not to meet the above threshold.

Recently Adopted Accounting Pronouncements

ASU 2021-10: Government Assistance

In November 2018, the Financial Accounting Standards Board (“FASB”) issued ASU 2021-10, Government Assistance (Topic 832) which discussed the requirements for disclosures, to be applied prospectively or retrospectively, related to transactions with a government. ASU 2021-10 is effective for fiscal years beginning after December 15, 2021. The new disclosure requirements required disclosures around 1) information about the nature of the transactions and the related accounting policy used to account for the transactions, 2) the line items on the balance sheet and income statement that are affected by the transactions, and the amounts applicable to each financial statement line item, and 3) significant terms and conditions of the transactions, including commitments and contingencies. The Company currently includes information on government grants and the adoption of ASU 2021-10 on January 1, 2022 has not had a material impact on the Company’s consolidated financial statements.

Results of Operations

The following table presents a comparison of the twelve months ended December 31, 2022, 2021 and 2020.

	Year ended December 31,				
	2022	2021	2020	2022 vs 2021	2021 vs 2020
	(in thousands)				
Total revenues	\$ 106,483	\$ 524,002	\$ 37,514	\$ (417,519)	\$ 486,488
Operating expenses:					
Cost of revenues	(3,343)	(24,976)	—	21,633	(24,976)
Research and development expenses	(197,591)	(143,548)	(122,400)	(54,043)	(21,148)
Selling, general and administrative expenses	(55,059)	(56,290)	(42,580)	1,231	(13,710)
Total operating expenses	(255,993)	(224,814)	(164,980)	(31,179)	(59,834)
Other income	7,171	12,306	3,342	(5,135)	8,964
Other expense	(820)	(876)	(1,302)	56	426
(Loss) / income from operations	(143,159)	310,618	(125,426)	(453,777)	436,044
Non-operating items, net	14,900	22,188	(16,017)	(7,288)	38,205
(Loss) / income before income tax benefit / (expense)	\$ (128,259)	\$ 332,806	\$ (141,443)	(461,065)	474,249
Income tax benefit / (expense)	1,470	(3,217)	16,419	4,687	(19,636)
Net (loss) / income	\$ (126,789)	\$ 329,589	\$ (125,024)	\$ (456,378)	\$ 454,613

Revenues and cost of revenues

Our revenue and associated costs for the years ended December 31, 2022, 2021 and 2020 was as follows:

	Year ended December 31,				
	2022	2021	2020	2022 vs 2021	2021 vs 2020
	(in thousands)				
License revenues	\$ 100,000	\$ 517,400	\$ 37,319	\$ (417,400)	\$ 480,081
Collaboration revenues	4,766	6,602	195	(1,836)	6,407
Contract manufacturing revenues	1,717	—	—	1,717	—
Total revenues	\$ 106,483	\$ 524,002	\$ 37,514	\$ (417,519)	\$ 486,488
Cost of license revenues	(1,254)	(24,976)	—	23,722	(24,976)
Cost of contract manufacturing revenues	(2,089)	—	—	(2,089)	—
Total cost	\$ (3,343)	\$ (24,976)	\$ —	\$ 21,633	\$ (24,976)

CSL Behring

We recognize license revenue in relation to the License Sale when it becomes probable that regulatory and sales milestone events will be achieved as well as when royalties on sales of Product have been earned. We recognized \$100.0 million and \$517.4 million of license revenue for the years ended December 31, 2022 and 2021. We recognized \$100.0 million of license revenue in 2022 related to a milestone payment we expect to collect following the first sale of HEMGENIX™ in the U.S. in 2023. We recognized \$517.4 million license revenue in 2021 related to the fixed upfront payment of \$450.0 million and the \$12.4 million we received in relation to the Additional Covenants after the Closing as well as a total of \$55.0 million of payments related to milestone payments owed on submission of the MAA in March 2022 and the BLA in April 2022, which we had considered probable as of the February 25, 2022 filing of the 2021 financial statements.

We expense contract fulfillment costs associated with license revenue recognized as costs of license contract revenues. These expenses primarily consist of payments we owe to our licensors in relation to license payments we receive from CSL Behring. We incurred \$1.3 million and \$25.0 million of such cost in the years ended December 31, 2022 and 2021, respectively. We did not incur such costs in the years ended December 31, 2020.

We recognize collaboration revenues associated with services rendered in relation to completing the HOPE-B clinical trial on behalf of CSL Behring between Closing and December 2022, when CSL Behring fully assumed these activities as well as in relation to additional development services that CSL Behring requests. These services are provided by our employees. Collaboration revenue related to these contracted services is recognized when the performance obligations are satisfied.

We recognized \$3.0 million, \$2.4 million, and nil of collaboration revenue for the years ended December 31, 2022, 2021 and 2020, respectively. The increase in collaboration revenue in 2022 of \$0.6 million compared to 2021 was primarily related to revenues related to full-time-employee (“FTE”) recharges of \$3.0 million recognized from the CSL Behring agreement as a result of additional development services that CSL Behring requested.

We recognize contract manufacturing revenue related to contract manufacturing HEMGENIX™ for CSL Behring. Contract manufacturing revenue is realized when earned upon sales of HEMGENIX™ to CSL Behring. We recognized \$1.7 million contract manufacturing revenues in the year ended December 31, 2022. We did not recognize such revenues in 2021 and 2020, as we started contract manufacturing activities to supply CSL Behring with launch supplies of HEMGENIX™ following their submission of a BLA and MAA in the spring of 2022.

We incurred \$2.1 million of cost of contract manufacturing revenues related to the manufacture of the Product in the year ended December 31, 2022, compared to nil cost of contract manufacturing revenues in the years ended December 31, 2021 and 2022, respectively.

BMS

We recognized license revenues associated with the amortization of the non-refundable upfront payment and target designation fees we received from BMS in 2015 until December 1, 2020. 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 of \$27.8 million as of December 1, 2020 as license revenue from a related party. On December 17, 2020 BMS designated one of the four Collaboration Targets as a candidate to advance into IND-enabling studies under the amended BMS CLA entitling us to receive a \$4.4 million research milestone payment, which we recorded as license revenue in the year ended December 31, 2020. We recognized no license revenues in the years ended December 31, 2022 and December 31, 2021.

We recognized collaboration revenues associated with Collaboration Target-specific pre-clinical analytical development and process development activities that were 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 were recognized when performance obligations were satisfied. We recognized \$1.8 million, \$4.2 million and, \$0.2 million of collaboration revenue for the years ended December 31, 2022, 2021 and 2020, respectively.

Following the termination of the amended BMS CLA on February 22, 2023 we do not expect to recognize any further revenue for services rendered in accordance with the BMS CLA.

Research and development expenses

We expense 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 development and improvement of our manufacturing processes and methods;
- costs associated with research activities for enabling technology platforms, such as next-generation vectors, promoters and re-administration of gene therapies;
- costs associated with the rendering of collaboration services as well as the continued development of the Product;
- payments related to identifiable intangible assets without an alternative future use;
- payments to our licensors for milestones that have been achieved related to our product candidates, including approval of the BLA;
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other supplies; and
- changes in the fair value of liabilities recorded in relation to our acquisition of Corlieve.

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

- *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. Since 2021, we have also incurred costs related to our Phase Ib/II clinical trial in Europe;
- *AMT-260 (Temporal lobe epilepsy)*. We have incurred costs related the preclinical development of temporal lobe epilepsy, which we acquired from Corlieve on July 30, 2021;
- *AMT-191 (Fabry disease)*. We have incurred costs related to the preclinical development of Fabry disease;

- *Etranacogene dezaparovec (hemophilia B)*. We have incurred costs related to the research, development, and production of etranacogene dezaparovec for the treatment of hemophilia B. During 2020 and up to the Closing of the CSL Behring Agreement we incurred costs related to the preparation of a BLA and MAA and for commercialization of the Product. We also incurred costs for manufacturing development. After the Closing, CSL Behring is responsible for the clinical and regulatory development and commercialization of the Product;
- *Preclinical research programs*. We incurred 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 incurred 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 judgment 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, 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, 2022 were \$197.6 million, compared to \$143.5 million and \$122.4 million for the years ended December 31, 2021 and 2020, 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,				
	2022	2021	2020	2022 vs 2021	2021 vs 2020
	(in thousands)				
Huntington's disease (AMT-130)	\$ 19,846	\$ 10,529	\$ 6,905	\$ 9,317	\$ 3,624
Temporal lobe epilepsy (AMT-260)	16,199	913	—	15,286	913
Fabry disease (AMT-191)	2,862	859	749	2,003	110
Hemophilia B (AMT-060/061)	2,474	8,738	21,458	(6,264)	(12,720)
Programs in preclinical development and platform related expenses	7,157	7,986	5,769	(829)	2,217
Total direct research and development expenses	\$ 48,538	\$ 29,025	\$ 34,881	\$ 19,513	\$ (5,856)
Employee and contractor-related expenses	64,935	55,725	41,694	9,210	14,031
Facility expenses	23,582	18,796	17,390	4,786	1,406
Share-based compensation expenses	18,402	12,822	11,995	5,580	827
Disposables	17,830	14,679	10,203	3,151	4,476
Other expenses	17,223	5,818	6,237	11,405	(419)
Fair value changes related to contingent consideration	7,081	6,683	—	398	6,683
Total other research and development expenses	\$ 149,053	\$ 114,523	\$ 87,519	\$ 34,530	\$ 27,004
Total research and development expenses	\$ 197,591	\$ 143,548	\$ 122,400	\$ 54,043	\$ 21,148

Direct research and development expenses

Huntington disease (AMT-130)

We incurred \$19.8 million, \$10.5 million and \$6.9 million in the years ended December 2022, 2021 and 2020 respectively. In the year ended December 31, 2022, our external costs for the development of AMT-130 were primarily related to the execution of our Phase I/II clinical trial in the U.S. and in Europe. In the years ended December 31, 2021 and December 31, 2020 our external costs for the development of AMT-130 were primarily related to the execution of our Phase I/II clinical trial in the U.S. and in the year ended December 31, 2021, costs were incurred for the preparation of the Phase I/Ib clinical trial in Europe.

Temporal lobe epilepsy (AMT-260)

In years ended December 31, 2022, December 31, 2021 and December 31, 2020, we incurred \$16.2 million, \$0.9 million and nil, respectively, for the preclinical development of temporal lobe epilepsy, which we acquired from Corlieve on July 30, 2021. The increase in development cost in the year ended December 31, 2022 related to cost incurred in relation to a toxicology study as well as manufacturing supplies for clinical development.

Fabry disease (AMT-191)

In the years ended December 31, 2022 December 31, 2021 and December 31, 2020, we incurred \$2.9 million, \$0.9 million and \$0.7 million, respectively, primarily related to our preclinical activities for the treatment of Fabry disease (AMT-191).

Hemophilia B (AMT-060/061)

In the years ended December 31, 2022, December 31, 2021 and December 31, 2020, the external costs for our hemophilia B program were primarily related to the execution of our Phase III clinical trial and Manufacturing Development. During 2020 and up to the Closing of the CSL Behring Agreement in May 2021, we also incurred costs related to the preparation of the global regulatory submissions and to prepare for commercialization of the Product. After the Closing, CSL Behring is responsible for the clinical and regulatory activities and commercialization of the Product. We managed the existing trials on behalf of CSL Behring until December 2022, at which point the trials began to be managed by CSL Behring. Direct research and development expenses related to clinical development incurred in the year ended December 31, 2022 and 2021 are presented net of reimbursements due from CSL Behring.

In the same periods, we also incurred costs related to the long-term follow-up of patients in our Phase I/II clinical trial of AMT-060 and our Phase I Ib clinical trial of etranacogene dezaparvovec. Our Phase I Ib 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. These costs are presented net of reimbursements due from CSL Behring.

Preclinical programs & platform development

In the year ended December 31, 2022, we incurred \$7.2 million of costs primarily related to our preclinical activities associated with product candidates for various other research programs and technology innovation projects.

In the year ended December 31, 2021, we incurred \$8.0 million of costs related to related to our preclinical activities for product candidates including SCA3 (AMT-150) as well as various other research programs and technology innovation projects compared to \$5.8 million in 2020. Costs for the year ended December 31, 2020 also include costs for Hemophilia A (AMT-180), which was deprioritized in June 2020.

Other research & development expenses

- We incurred \$64.9 million in employee and contractor expenses in the year ended December 31, 2022 compared to \$55.7 million in 2021 and \$41.7 million in 2020. Our cost increased in 2022 by \$9.2 million compared to 2021 primarily as a result of an increase in personnel and contractor related expenses to support our growth. Costs increased by \$14.0 million in 2021 compared to 2020 as a result of the recruitment of personnel to support the preclinical and clinical trial development of our product candidates;
- We incurred \$23.6 million in operating expenses and depreciation expenses related to our rented facilities in the year ended December 31, 2022 compared to \$18.8 million in 2021 and \$17.4 million in 2020. The increase in 2022 compared to 2021 of \$4.8 million primarily related to additional sites in Lexington and increased depreciation expense related to the expansion of the Amsterdam facility in prior year. The increase in 2021 compared to 2020 of \$1.4 million primarily related to expansion of the Amsterdam facility;
- We incurred \$17.8 million in disposables costs in the year ended December 31, 2022 compared to \$14.7 million in the year ended December 31, 2021 and \$10.2 million in the year ended December 31, 2020. The increases are primarily related to the expansion of our activities to support the development of our product candidates;
- We incurred \$18.4 million in share-based compensation expenses in the year ended December 31, 2022 compared to \$12.8 million in 2021 and \$12.0 million in 2020. The increase in 2022 compared to 2021 of \$5.6 million was primarily driven by the increase in awards granted, including those to newly recruited personnel as well as an increase in expense related to performance share units that were deemed probable. The increase in 2021 compared to 2020 of \$0.8 million was driven primarily by grants to newly recruited personnel offset by share-based compensation expenses recorded in relation to the termination of one of our executives in 2020;
- We incurred \$17.2 million in other expenses in the year ended December 31, 2022 compared to \$5.8 million in 2021 and \$6.2 million in 2020. The increase in 2022 compared to 2021 of \$11.4 million is primarily due to \$7.0 million of contractual payments we owed to licensors upon FDA approval of HEMGENIX™ and \$1.1 million owed to a licensor for a valid patent claim granted within the EU. The decrease in 2021 compared to 2020 of \$0.4 million is a combination of not incurring any expenses related to license payments without an alternative future use like in 2020 (\$3.4 million) offset by various increases, including increases in professional fees as a result of expanding the organization and to support the cGMP validation of our Lexington facility; and
- We incurred \$7.1 million of expenses for the year ended December 31, 2022 related to an increase in the fair value of contingent consideration associated with the Corlieve Transaction, compared to \$6.7 million and nil for the same periods in 2021 and 2020.

Selling, general and administrative expenses

Our general and administrative expenses consist principally of employee, office, consulting, legal and other professional and administrative expenses. We incurred 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 and advisory fees related to obtaining the CSL Behring Agreement.

Selling, general and administrative expenses for the year ended December 31, 2022 were \$55.1 million, compared to \$56.3 million and \$42.6 million for the years ended December 31, 2021 and 2020, respectively.

- We incurred \$21.1 million in personnel and contractor expenses in 2022 compared to \$16.0 million in 2021 and \$13.6 million in 2020. The increase in 2022 of \$5.0 million, compared to 2021, and the increase in 2021 compared to 2020 of \$2.4 million was primarily driven by an increase in personnel and contractor related expenses to support our growth;

- We incurred \$15.5 million of share-based compensation expenses in 2022 compared to \$12.8 million in 2021 and \$9.8 million in 2020. The increase in 2022 compared to 2021 of \$2.7 million was primarily related to the increase in awards granted, including those to newly recruited personnel as well as an increase in expense related to performance share units that were deemed probable. The increase in 2021 compared to 2020 of \$3.0 million was also primarily driven by the increase in awards granted including those to newly recruited personnel;
- We incurred \$7.1 million in professional fees in 2022 compared to \$9.4 million in 2021 and \$8.0 million in 2020. We regularly incur accounting, audit and legal fees associated with operating as a public company. Additionally, in the years ended December 31, 2021 and December 31, 2020, we incurred professional fees in relation to our licensing transaction with CSL Behring and our acquisition of Corlieve; and
- We incurred \$1.0 million, \$5.1 million and nil in financial advisory fees in relation to our licensing transaction with CSL Behring in the years ended December 31, 2022, December 31, 2021 and December 31, 2020. These fees are calculated as a percentage of license revenue recognized under the CSL Behring Agreement.

Other items, net

We recognized \$0.3 million, \$3.0 million and nil in other income in relation to the equity stake received in VectorY B.V. in conjunction with a settlement agreement that the Company and VectorY B.V. entered into in April 2021 for the years ended December 31, 2022, 2021 and 2020, respectively.

We recognized nil in other income of employee retention credit under the U.S. CARES Act in the year ended December 31, 2022, compared to \$2.6 million and nil such income for the same periods in 2021 and 2020, respectively.

In 2022, we recognized \$5.6 million in income related to payments received from European authorities to subsidize our research and development efforts in the Netherlands compared to \$5.3 million in 2021 and \$1.9 million in 2020.

Other income for the years ended December 31, 2022, 2021 and 2020 also includes 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

Our non-operating items, net, for the years ended December 31, 2022, 2021 and 2020 were as follows:

	Year ended December 31,				
	2022	2021	2020	2022 vs 2021	2021 vs 2020
	(in thousands)				
Interest income	\$ 609	\$ 162	\$ 938	\$ 447	\$ (776)
Interest expense	(11,704)	(7,474)	(3,825)	(4,230)	(3,649)
Foreign currency gains / (losses), net	23,235	29,660	(13,613)	(6,425)	43,273
Other non-operating gains / (losses)	2,760	(160)	483	2,920	(643)
Total non-operating income, net	\$ 14,900	\$ 22,188	\$ (16,017)	\$ (7,288)	\$ 38,205

We recognize interest income associated with our cash and cash equivalents and investment securities. We recognized \$0.6 million interest income in 2022, \$0.2 million in 2021 and \$0.9 million in 2020. Our interest income increased in 2022 by \$0.4 million compared to 2021 primarily due to the interest income earned on investment securities. Interest income decreased by \$0.7 million in 2021 compared to 2020 due to a changes in market interest rates during 2021.

We recognized \$11.7 million interest expense in 2022, \$7.5 million in 2021 and \$3.8 million in 2020. Our interest expense in 2022 primarily increased by \$4.2 million compared to 2021 due to an increase in market interest rates in 2022. Our interest expense in 2021 primarily increased by \$3.6 million compared to 2020 due to the additional \$35.0 million we drew down on our loan facility from Hercules in January 2021.

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. In 2022, we recognized a net foreign currency gain of \$23.2 million related to our borrowings from Hercules and our cash and cash equivalents and investment securities as well as loans between entities within the uniQure group, compared to a net gain of \$29.7 million in 2021 and a net loss of \$13.6 million in 2020.

In 2022, we recognized a \$2.8 million net gain within Other non-operating gains / (losses) related to a decrease in the fair value market value of derivative financial liability related to the change of control payment (“CoC-payment”) compared to a net loss of \$0.2 million in 2021 and a net gain of \$0.5 million in 2020. We recorded the net gain in 2022 as no change of control event had occurred as of the February 22, 2023 Termination Date of the amended BMS CLA. We had recorded a net loss in 2021 of \$0.2 million in 2021 for the increase in the fair market value of the derivative financial liability related to the CoC-payment. We recorded a net gain \$0.5 million in 2020 within Other non-operating gains / (losses) related to the net impact of terminating the BMS warrants and recognizing a derivative financial liability for the CoC-payment.

Income tax

We recognized \$1.5 million of deferred tax income in 2022, compared to \$3.2 million of deferred tax expense in 2021 and \$16.4 million of deferred tax income in 2020. Deferred tax income recorded in 2022 results from deferred tax benefits recorded related to the buildup of net operating losses by the French entity which are partially offset by deferred tax expense recorded in the U.S. as a result of the consumption of net operating losses as well as deferred tax expense resulting from the release of valuation allowance for the tax benefit of share issuance costs within the Netherlands. Deferred tax expense recorded in 2021 results from the consumption of net operating tax losses by our U.S. entity as well as deferred tax expense resulting from the release of valuation allowance for the tax benefit of share issuance costs within the Netherlands. 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.

Financial Position, Liquidity and Capital Resources

As of December 31, 2022, we had cash and cash equivalents, restricted cash and investment securities of \$396.0 million. 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 believe that our cash and cash equivalents and investment securities will fund our operations into 2025 assuming the achievement of \$100.0 million of first commercial sale milestone in the U.S. and into the first half of 2025 if the \$75.0 million first commercial sale milestone in any of the five contractually defined European countries would be achieved prior to July 2, 2023 under the CSL Behring Agreement. Our material cash requirements include the following contractual and other obligations:

Debt

As of December 31, 2022, we had an outstanding loan amount owed to Hercules for an aggregate principal amount of \$100.0 million. Future interest payments and financing fees associated with the loan total \$44.5 million, with \$14.9 million payable within 12 months. We are contractually required to repay the \$100.0 million in full in December 2025.

Leases

We entered into lease arrangements for facilities, including corporate, manufacturing and office space. As of December 31, 2022, we had fixed lease payment obligations of \$60.6 million, with \$8.3 million payable within 12 months.

Commitments related to Corlieve acquisition (nominal amounts)

In relation to the Corlieve Transaction, we entered into commitments to make payments to the former shareholders upon the achievement of certain contractual milestones. The commitments include payments related to post-acquisition services that we agreed to as part of the SPA. As of December 31, 2022, our commitment amounts include up to \$42.8 million in potential milestone payments through Phase I/II development and \$171.3 million in potential milestone payments associated with Phase III development and the approvals of AMT-260 in the U.S. and EU. The timing of achieving these milestones and consequently the timing of payments, as well as whether the milestone will be achieved at all, is generally uncertain. These payments are owed in Euro and have been translated at the foreign exchange rate as of December 31, 2022, of \$1.07/€1.00. As of December 31, 2022, we expect these obligations will become payable between 2023 and 2031. If and when due, up to 25% of the milestone payments can be settled with our ordinary shares.

Commitments related to licensors and financial advisors

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 BLA, approval by the FDA or product launch) or as a result of collecting payments related to our License Sale to CSL Behring. We also owe payments to a financial advisor related to any payments we will collect under the CSL Behring Agreement.

The table below summarizes our consolidated cash flow data for the years ended December 31:

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Cash, cash equivalents and restricted cash at the beginning of the period	\$ 559,353	\$ 247,680	\$ 380,726
Net cash (used in) / generated from operating activities	(145,060)	287,959	(134,828)
Net cash used in investing activities	(182,734)	(67,387)	(9,484)
Net cash generated from financing activities	1,445	94,858	7,444
Foreign exchange impact	(1,831)	(3,757)	3,822
Cash, cash equivalents and restricted cash at the end of period	\$ 231,173	\$ 559,353	\$ 247,680

We had previously incurred losses and cumulative negative cash flows from operations since our business was founded by our predecessor entity AMT Holding N.V. in 1998, with the exception of generating income in 2021 after receiving the upfront payment upon Closing of the CSL Behring Agreement. We continue to incur losses in the current period. We recorded a net loss of \$126.8 million for the year ended December 31, 2022, and net income of \$329.6 million in 2021, and a net loss of \$125.0 million in 2020. As of December 31, 2022, we had an accumulated deficit of \$581.9 million.

Sources of liquidity

From our first institutional venture capital financing in 2006 through May 2021, we funded our operations primarily through private and public placements of equity securities and convertible and other debt securities as well as payments from our collaboration partners. In May 2021, we received a \$462.4 million cash payment due from CSL Behring upon Closing. During 2022 we collected the \$55.0 million related to CSL Behring's global regulatory submissions for etranacogene dezaparvoec in March and April 2022 and are eligible to receive additional milestone payments, as well as royalties on net sales, from CSL Behring.

On March 1, 2021, we entered into a Sales Agreement with SVB Leerink LLC ("SVB Leerink") with respect to an at-the-market ("ATM") offering program, under which we may, from time to time in our sole discretion, offer and sell through SVB Leerink, acting as agent, our ordinary shares, up to an aggregate offering price of \$200.0 million. We will pay SVB Leerink a commission equal to 3% of the gross proceeds of the sales price of all ordinary shares sold through it as a sales agent under the Sales Agreement. In the year ended December 30, 2021, we received net proceeds of \$29.6 million from the issuance of 921,730 ordinary shares under the Sales Agreement that took place during March and April of that year. We did not issue in ordinary shares under the Sales Agreement for the 12 month period ended December 31, 2022.

On January 29, 2021, we drew down \$35 million under a facility agreement with Hercules. We drew down a further \$30 million under our 2021 Restated Facility with Hercules in December 2021.

We are subject to certain covenants under our 2021 Restated 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 2021 Restated Facility may limit our ability to obtain debt financing. The 2021 Restated Facility permits us to issue up to \$500.0 million of convertible debt as well as to enter into a transaction to sell the royalties under the CSL Behring agreement subject to certain conditions.

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 / generated from operating activities

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Cash flows from operating activities			
Net (loss) / income	\$ (126,789)	\$ 329,589	\$ (125,024)
Adjustments to reconcile net (loss) / income to net cash (used in) / generated from operating activities:			
Depreciation and amortization	8,537	7,299	10,648
Share-based compensation expenses	34,204	25,635	21,831
Deferred tax (income) / expense	(1,470)	3,210	(16,419)
Change in fair value of contingent consideration and derivative financial instruments, net	4,320	6,843	(483)
Unrealized foreign exchange (gains) / losses, net	(22,083)	(31,335)	14,730
Change in deferred revenue	-	-	(33,642)
Other non-cash items, net	1,605	(2,800)	-
Changes in operating assets and liabilities:			
Accounts receivable, prepaid expenses, and other current assets and receivables	(4,083)	(3,959)	(6,967)
Contract asset related to CSL Behring milestone payments	(45,000)	(55,000)	-
Inventories	(6,924)	-	-
Accounts payable	9,238	(727)	(2,701)
Accrued expenses, other liabilities, and operating leases	3,385	9,204	3,199
Net cash (used in) / generated from operating activities	<u>\$ (145,060)</u>	<u>\$ 287,959</u>	<u>\$ (134,828)</u>

Net cash used in operating activities was \$145.1 million for the year ended December 31, 2022, and consisted of a net loss of \$126.8 million adjusted for non-cash items, including depreciation and amortization expense of \$8.5 million, share-based compensation expense of \$34.2 million, changes in the fair value of contingent consideration and the derivative financial liability of \$4.3 million, unrealized foreign exchange gains of \$22.1 million and a change in deferred taxes of \$1.5 million. Net cash generated from operating activities also included unfavorable changes in operating assets and liabilities of \$43.4 million. There was a net increase in accounts receivable, prepaid expenses, and other current assets and receivables of \$4.1 million. There was a net increase in contract assets related to CSL Behring milestone payments of \$45.0 million. The net increase related to \$100.0 million recognized as a contract asset in the current period and collection of \$55.0 million of the contract asset related to the CSL milestones of \$55.0 million in March 2022 and April 2022. There was an increase in inventories of \$6.9 million related to the production of HEMGENIX™ under the CSL Behring Agreement. These changes also relate to a net increase in accounts payable, accrued expenses, other liabilities, and operating leases of \$12.6 million, primarily related to an increase in accounts payable.

Net cash generated from operating activities was \$288.0 million for the year ended December 31, 2021, and consisted of net income of \$329.6 million adjusted for non-cash items, including depreciation and amortization expense of \$7.3 million, share-based compensation expense of \$25.6 million, a change in fair value of contingent consideration of \$6.8 million, unrealized foreign exchange gains of \$31.3 million, a change in deferred taxes of \$3.2 million and other non-cash items, net, of \$2.8 million. Net cash generated from operating activities also included unfavorable changes in operating assets and liabilities of \$50.3 million, which includes \$55.0 million recognized as a contract asset related to probable CSL Behring milestone payments. Additionally, these changes also related to a net increase in accounts receivable, prepaid expenses, and other current assets and receivables of \$4.0 million primarily related to an increase in various prepaids, including those related to clinical trials, partially offset by decrease in receivables as a result of collection of the BMS milestone that was recorded as of December 31, 2020 and collection of the CSL Behring receivables recorded as of December 31, 2020 for expenses for which we had a right of reimbursement and a net increase in accounts payable, accrued expenses, other liabilities, and operating leases of \$8.5 million primarily related to an increase in various accruals for goods received from and services provided by vendors and an increase in personnel accruals. Net income primarily consisted of \$462.4 million license revenue recognized on Closing and \$55.0 million license revenue related to CSL Behring's global regulatory submissions for etranacogene dezaparvovec that occurred in March and April 2022 and were considered probable on December 31, 2021.

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 investing activities

In 2022, we used \$182.7 million in our investing activities compared to \$67.4 million in 2021 and \$9.5 million in 2020.

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Investment in investment securities	\$ (163,146)	\$ —	\$ —
Build out of Amsterdam site	(11,904)	(12,412)	(4,534)
Build out of Lexington site	(5,784)	(5,026)	(2,737)
Acquisition of Corlieve, net of cash acquired	(1,900)	(49,949)	—
Acquisition of licenses, patents, and other rights	—	—	(2,213)
Total investments	\$ (182,734)	\$ (67,387)	\$ (9,484)

In 2022, we invested \$163.1 million of our cash on hand into euro and dollar denominated government bonds. We made no such investments in 2021 and 2020.

In 2022, we invested \$11.9 million in the build out of our Amsterdam site compared to \$12.4 million in 2021 and \$4.5 million in 2020. Our investments in 2022 related to investments into equipment while in 2021 investments primarily related to the construction of additional laboratories to support the expansion of our research and development activities as well as the construction of a cleanroom designed to be capable of manufacturing cGMP materials at a 500-liter scale.

In 2022, we invested \$5.8 million in our facility in Lexington compared to \$5.0 million in 2021 and \$2.7 million in 2020. Our investments in 2022 increased as a result of the two new Lexington sites, which commenced in 2022.

We paid EUR 1.8 million (\$1.9 million) to acquire the remaining outstanding shares of Corlieve in February, July and September 2022. We paid EUR 42.1 million (\$49.9 million), net of EUR 2.8 million (\$3.3 million) of cash acquired, during the year ended December 31, 2021 to acquire 97.7% of the outstanding ordinary shares of Corlieve on July 30, 2021.

Net cash generated from financing activities

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Cash flows from financing activities			
Proceeds from issuance of shares related to employee stock option and purchase plans	\$ 1,445	\$ 2,798	\$ 7,444
Proceeds from loan increment, net of debt issuance costs	-	64,067	-
Proceeds from issuance of ordinary shares, net of issuance costs	-	29,565	-
Repayment of debt assumed through Corlieve Transaction	-	(1,572)	-
Net cash generated from financing activities	\$ 1,445	\$ 94,858	\$ 7,444

In 2022, we received \$1.4 million from the exercise of options to purchase ordinary shares issued in accordance with our share incentive plans, compared to \$2.8 million in 2021 and \$7.4 million in 2020.

In January 2021, we received \$34.6 million net proceeds from the 2021 Amended Facility and in December 2021 we received \$29.5 million net proceeds from the 2021 Restated Facility for combined net proceeds of \$64.1 million (nil in 2020 and 2022).

We received net proceeds of \$29.6 million associated with our ATM offering in March and April 2021. No such proceeds were received in 2022 or 2020.

Upon the acquisition of Corlieve, Corlieve held loans with an outstanding amount equal to EUR 1.4 million (\$1.6 million). During the year ended December 31, 2021, the loans were repaid in their entirety.

Funding requirements

We believe that our cash and cash equivalents and investment securities will fund our operations into 2025 assuming the achievement of \$100.0 million of first commercial sale milestone in the U.S. and into the first half of 2025 if the \$75.0 million first commercial sale milestone in any of the five contractually defined European countries would be achieved prior to July 2, 2023 under the CSL Behring Agreement. Our future capital requirements will depend on many factors, including but not limited to:

- contractual milestone payments and royalties we might be owed in accordance with the CSL Behring Agreement;
- earnout payments we might owe the former shareholders of Corlieve, which are subject to the achievement of specific development and regulatory milestones;
- the scope, timing, results, and costs of our current and planned clinical trials, including those for AMT-130 in Huntington's disease;
- the extent to which we acquire or in-license other businesses, products, product candidates or technologies;
- the amount and timing of revenue, if any, we receive from manufacturing products for CSL Behring;
- 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 costs associated with maintaining quality compliance and optimizing our manufacturing processes, including the operating costs associated with our Lexington, Massachusetts manufacturing facility; and
- the costs associated with increasing the scale and capacity of our manufacturing capabilities.

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 and the Swiss Franc. As our U.S. operating entity primarily conducts its operations in U.S. dollars, its exposure to changes in foreign currency is insignificant. Similarly, the exposure to changes in foreign currencies of our Swiss and French entities are insignificant as well.

Our Dutch entities hold significant amounts of U.S. dollars in cash and cash equivalents and investment securities, 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 or loss. On December 31, 2022, if the euro had weakened 10% against the U.S. dollar with all other variables held constant, pre-tax loss for the year would have been \$20.4 million lower (December 31, 2021: pre-tax income \$42.2 million higher), and other comprehensive income or loss would have been \$24.4 million higher (December 31, 2021: \$23.5 million higher). Conversely, if the euro had strengthened 10% against the U.S. dollar with all other variables held constant, pre-tax loss for the year would have been \$20.4 million higher (December 31, 2021: pre-tax income \$42.2 million lower), and other comprehensive income or loss would have been \$32.1 million lower (December 31, 2021: \$31.6 million lower).

We strive to mitigate foreign exchange risk through holding sufficient funds in euro and dollars to finance budgeted cash flows for generally 18 months.

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 and investment securities.

In June 2013, we entered into the Hercules Agreement, which was last amended and restated in December 2021, 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, 2022, the loan bore an interest rate of 12.2%.

As of December 31, 2022, 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 \$1.0 million lower (2021: \$0.7 million lower; 2020: \$0.3 million lower.)

We invest in government debt in accordance with our investment policy. We are exposed to interest rate risk as market interest rates could differ from the interest rates that we fix at the time of acquiring these investment securities. As we intend to hold these to maturity, we do not recognize changes in the fair value of our investment which are caused by changes in market interest rates.

This means that a change in prevailing interest rates may cause the fair value of the investment to fluctuate. For example, if we hold a security that was issued at a fixed interest rate at the then-prevailing rate and the prevailing interest rate later rises, the fair value of our investment will probably decline.

The average duration of all of our investment securities held as of December 31, 2022, was less than 14 months. Due to the relatively short-term nature of these financial instruments and our ability and intention to hold these investments to maturity, we believe there is no material exposure to interest rate risk.

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 and CSL Behring.

We deposited funds as security to our landlord related to 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. We also have short- and long-term investment securities in U.S. and European government bonds maturing within three to 14 months. Our investment policy requires us to invest with counterparties with the highest investment credit rating. Due to the high credit quality of our counterparties, we believe there is no material exposure to credit risk in our portfolio of investment securities.

Liquidity Risk

We believe that our cash and cash equivalents and investment securities will fund our operations into 2025 assuming the achievement of \$100.0 million of first commercial sale milestone in the U.S. and into the first half of 2025 if the \$75.0 million first commercial sale milestone in any of the five contractually defined European countries would be achieved prior to July 2, 2023 under the CSL Behring Agreement. 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 (in thousands)	Between 3 - 5 years	Over 5 years
At December 31, 2022					
Long-term debt	\$ —	\$ 14,870	\$ 129,622	\$ —	\$ —
Accounts payable, accrued expenses and other current liabilities	—	41,555	—	—	—
Commitments related to Corlieve acquisition (maximum nominal amounts)	214,070	—	—	—	—
Total	\$ 214,070	\$ 56,425	\$ 129,622	\$ —	\$ —
At December 31, 2021					
Long-term debt	\$ —	\$ 7,984	\$ 26,054	\$ 101,549	\$ —
Accounts payable, accrued expenses and other current liabilities	—	30,989	—	—	—
Derivative financial instruments	2,805	—	—	—	—
Commitments related to Corlieve acquisition (maximum nominal amounts)	226,862	2,269	—	—	—
Total	\$ 229,667	\$ 41,242	\$ 26,054	\$ 101,549	\$ —

During the year ended December 31, 2021, we recorded an amount for the derivative financial liability related to the CoC-payment under the amended BMS CLA. Generally, the CoC-payment would have been 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 had no contractual maturity date for the year ended December 31, 2021. We released the derivative financial liability during the year ended December 31, 2022 as a result of the termination of the amended BMS CLA as of February 22, 2023.

In relation to the Corlieve Transaction, we entered into commitments to make payments to the former shareholders upon the achievement of certain contractual milestones. The commitments include payments related to post-acquisition services that we agreed to as part of the SPA. The timing of achieving these milestones, as well as whether the milestone will be achieved at all, and consequently the timing of payments is generally uncertain with the exception of payments we owed upon acquiring the remaining outstanding shares as well as certain payments for post-acquisition services made in 2022. We expect these obligations will become payable between 2023 and 2031. If and when due, up to 25% of the milestone payments can be settled with our ordinary shares.

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.

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”, our principal executive officer) and chief financial officer (“CFO”, our principal financial officer), evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2022. Based on such evaluation, our CEO and CFO have concluded that as of December 31, 2022, 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, 2022. This assessment was performed under the direction and supervision of our CEO and CFO 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, 2022, 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, 2022. Their report is filed within this Annual Report on Form 10-K.

Inherent Limitations of Internal Controls

Our management, including our CEO and CFO, 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 2022, 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.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

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 2023 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 2023 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 2023 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 2023 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 2023 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:

	<u>Page</u>
Report of Independent Registered Public Accounting Firm – KPMG Accountants N.V.	100
Consolidated Balance Sheets as of December 31, 2022 and 2021	102
Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2022, 2021 and 2020	103
Consolidated Statements of Shareholders' Equity for the Years Ended December 31, 2022, 2021 and 2020	104
Consolidated Statements of Cash Flows for the Years Ended December 31, 2022, 2021 and 2020	105
Notes to Consolidated Financial Statements for the Years Ended December 31, 2022, 2021 and 2020	106

- (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, 2022, 2021 AND 2020

	<u>Page</u>
Report of Independent Registered Public Accounting Firm - KPMG Accountants N.V., Amstelveen, The Netherlands (PCAOB ID 1012)	100
Consolidated Balance Sheets as of December 31, 2022 and 2021	102
Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2022, 2021 and 2020	103
Consolidated Statements of Shareholders' Equity for the Years Ended December 31, 2022, 2021 and 2020	104
Consolidated Statements of Cash Flows for the Years Ended December 31, 2022, 2021 and 2020	105
Notes to Consolidated Financial Statements	106

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, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, shareholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2022, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the years in the three year-period ended December 31, 2022, 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, 2022 based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

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

Critical audit matters are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. We determined that there are no critical audit matters.

/s/ KPMG Accountants N.V.

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

Amstelveen, the Netherlands
February 27, 2023

uniQure N.V.

CONSOLIDATED BALANCE SHEETS

	December 31, 2022	December 31, 2021
	(in thousands, except share and per share amounts)	
Current assets		
Cash and cash equivalents	\$ 228,012	\$ 556,256
Current investment securities	124,831	—
Accounts receivable and contract asset	102,376	58,768
Inventories	6,924	-
Prepaid expenses	11,817	10,540
Other current assets and receivables	2,814	2,675
Total current assets	476,774	628,239
Non-current assets		
Property, plant and equipment, net	50,532	43,505
Non-current investment securities	39,984	—
Operating lease right-of-use assets	32,726	25,573
Intangible assets, net	58,778	62,686
Goodwill	25,581	27,633
Deferred tax assets, net	14,528	15,647
Other non-current assets	6,061	5,897
Total non-current assets	228,190	180,941
Total assets	\$ 704,964	\$ 809,180
Current liabilities		
Accounts payable	\$ 10,984	\$ 2,502
Accrued expenses and other current liabilities	30,571	28,487
Current portion of contingent consideration	25,982	—
Current portion of operating lease liabilities	8,382	5,774
Total current liabilities	75,919	36,763
Non-current liabilities		
Long-term debt	102,791	100,963
Operating lease liabilities, net of current portion	31,719	28,987
Contingent consideration, net of current portion	9,334	29,542
Deferred tax liability, net	8,257	12,913
Other non-current liabilities	935	4,236
Total non-current liabilities	153,036	176,641
Total liabilities	228,955	213,404
Commitments and contingencies		
Shareholders' equity		
Ordinary shares, €0.05 par value: 80,000,000 shares authorized as of December 31, 2022 and December 31, 2021 and 46,968,032 and 46,298,635 ordinary shares issued and outstanding as of December 31, 2022 and December 31, 2021, respectively	2,838	2,802
Additional paid-in-capital	1,113,393	1,076,972
Accumulated other comprehensive loss	(58,291)	(28,856)
Accumulated deficit	(581,931)	(455,142)
Total shareholders' equity	476,009	595,776
Total liabilities and shareholders' equity	\$ 704,964	\$ 809,180

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,		
	2022	2021	2020
	(in thousands, except share and per share amounts)		
License revenues	\$ 100,000	\$ 517,400	\$ 4,352
License revenues from related parties	—	—	32,967
Contract manufacturing revenues	1,717	—	—
Collaboration revenues	4,766	6,602	59
Collaboration revenues from related parties	—	—	136
Total revenues	106,483	524,002	37,514
Operating expenses:			
Cost of license revenues	(1,254)	(24,976)	—
Cost of contract manufacturing revenues	(2,089)	—	—
Research and development expenses	(197,591)	(143,548)	(122,400)
Selling, general and administrative expenses	(55,059)	(56,290)	(42,580)
Total operating expenses	(255,993)	(224,814)	(164,980)
Other income	7,171	12,306	3,342
Other expense	(820)	(876)	(1,302)
(Loss) / income from operations	(143,159)	310,618	(125,426)
Interest income	609	162	938
Interest expense	(11,704)	(7,474)	(3,825)
Foreign currency gains / (losses), net	23,235	29,660	(13,613)
Other non-operating gains / (losses), net	2,760	(160)	483
(Loss) / income before income tax benefit / (expense)	\$ (128,259)	\$ 332,806	\$ (141,443)
Income tax benefit / (expense)	1,470	(3,217)	16,419
Net (loss) / income	\$ (126,789)	\$ 329,589	\$ (125,024)
Other comprehensive loss:			
Foreign currency translation adjustments	(29,435)	(38,763)	16,596
Total comprehensive (loss) / gain	\$ (156,224)	\$ 290,826	\$ (108,428)
Earnings per ordinary share - basic			
Basic net (loss) / income per ordinary share	\$ (2.71)	\$ 7.17	\$ (2.81)
Earnings per ordinary share - diluted			
Diluted net (loss) / income per ordinary share	\$ (2.71)	\$ 7.04	\$ (2.81)
Weighted average shares - basic	46,735,045	45,986,467	44,466,365
Weighted average shares - diluted	46,735,045	46,840,972	44,466,365

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 income / (loss)	Accumulated deficit	Total shareholders' equity
	No. of shares	Amount				
	(in thousands, except share and per share amounts)					
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
Exercises 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
Income for the period	—	—	—	—	329,589	329,589
Other comprehensive loss	—	—	—	(38,763)	—	(38,763)
Issuance of ordinary shares	921,730	55	29,509	—	—	29,564
Income tax benefit of past share issuance cost	—	—	3,047	—	—	3,047
Exercises of share options	241,496	15	2,638	—	—	2,653
Restricted and performance share units distributed during the period	352,886	21	(21)	—	—	—
Share-based compensation expense	—	—	25,635	—	—	25,635
Issuance of ordinary shares relating to employee stock purchase plan	4,724	—	146	—	—	146
Balance at December 31, 2021	46,298,635	\$ 2,802	\$ 1,076,972	\$ (28,856)	\$ (455,142)	\$ 595,776
Loss for the period	—	—	—	—	(126,789)	(126,789)
Other comprehensive loss	—	—	—	(29,435)	—	(29,435)
Income tax benefit of past share issuance cost	—	—	808	—	—	808
Exercise of share options	152,356	8	1,272	—	—	1,280
Restricted and performance share units distributed during the period	505,799	27	(27)	—	—	—
Share-based compensation expense	—	—	34,204	—	—	34,204
Issuance of ordinary shares relating to employee stock purchase plan	11,242	1	164	—	—	165
Balance at December 31, 2022	46,968,032	\$ 2,838	\$ 1,113,393	\$ (58,291)	\$ (581,931)	\$ 476,009

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

uniQure N.V.
CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year ended December 31,		
	2022	2021 (in thousands)	2020
Cash flows from operating activities			
Net (loss) / income	\$ (126,789)	\$ 329,589	\$ (125,024)
Adjustments to reconcile net (loss) / income to net cash (used in) / generated from operating activities:			
Depreciation and amortization expense	8,537	7,299	10,648
Share-based compensation expense	34,204	25,635	21,831
Deferred tax (income) / expense	(1,470)	3,210	(16,419)
Changes in fair value of contingent consideration and derivative financial instrument, net	4,320	6,843	(483)
Unrealized foreign exchange (gains) / losses, net	(22,083)	(31,335)	14,730
Change in deferred revenue	-	-	(33,642)
Other non-cash items, net	1,605	(2,800)	-
Changes in operating assets and liabilities:			
Accounts receivable, prepaid expenses, and other current assets and receivables	(4,083)	(3,959)	(6,967)
Contract asset related to CSL Behring milestone payments	(45,000)	(55,000)	-
Inventories	(6,924)	-	-
Accounts payable	9,238	(727)	(2,701)
Accrued expenses, other liabilities, and operating leases	3,385	9,204	3,199
Net cash (used in) / generated from operating activities	<u>(145,060)</u>	<u>287,959</u>	<u>(134,828)</u>
Cash flows from investing activities			
Investment in investment securities	(163,146)	-	-
Purchases of property, plant, and equipment	(17,688)	(17,438)	(7,271)
Acquisition of Corlieve, net of cash acquired	(1,900)	(49,949)	-
Purchases of intangible assets	-	-	(2,213)
Net cash used in investing activities	<u>(182,734)</u>	<u>(67,387)</u>	<u>(9,484)</u>
Cash flows from financing activities			
Proceeds from issuance of ordinary shares related to employee stock option and purchase plans	1,445	2,798	7,444
Proceeds from loan increment, net of debt issuance costs	-	64,067	-
Proceeds from issuance of ordinary shares	-	30,899	-
Share issuance costs from issuance of ordinary shares	-	(1,334)	-
Repayment of debt acquired through acquisition of Corlieve	-	(1,572)	-
Net cash generated from financing activities	<u>1,445</u>	<u>94,858</u>	<u>7,444</u>
Currency effect on cash, cash equivalents and restricted cash	(1,831)	(3,757)	3,822
Net (decrease) / increase in cash, cash equivalents and restricted cash	<u>(328,180)</u>	<u>311,673</u>	<u>(133,046)</u>
Cash, cash equivalents and restricted cash at beginning of period	559,353	247,680	380,726
Cash, cash equivalents and restricted cash at the end of period	<u>\$ 231,173</u>	<u>\$ 559,353</u>	<u>\$ 247,680</u>
Cash and cash equivalents	\$ 228,012	\$ 556,256	\$ 244,932
Restricted cash related to leasehold and other deposits	3,161	3,097	2,748
Total cash, cash equivalents and restricted cash	<u>\$ 231,173</u>	<u>\$ 559,353</u>	<u>\$ 247,680</u>
Supplemental cash flow disclosures:			
Cash paid for interest	\$ (9,247)	\$ (6,539)	\$ (4,131)
Non-cash (decrease) / increase in accounts payables and accrued expenses and other current liabilities related to purchases of property, plant, and equipment	\$ (964)	\$ 1,488	\$ 630

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*) in Amsterdam, the Netherlands under number 54385229. The Company’s headquarters are in Amsterdam, the Netherlands, and its registered office is located at Paasheuvelweg 25, Amsterdam 1105 BP, the Netherlands and its telephone number is +31 20 240 6000. The Company’s website address is www.uniquire.com.

The Company’s ordinary shares are listed on the Nasdaq Global Select Market and trade 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 United States (“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, 2022 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 contingent consideration related to the acquisition of Corlieve Therapeutics SAS (“Corlieve”), the treatment of revenue to be recognized under the commercialization and license agreement entered into (“CSL Behring Agreement”) between the Company and CSL Behring LLC (“CSL Behring”), and the assessment of a valuation allowance on the Company’s deferred tax assets in the Netherlands and the U.S. 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. and Corlieve AG) 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 (\$) and the functional currency of Corlieve AG is the Swiss Franc (CHF). 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 7, "*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 Corlieve transaction

On June 21, 2021, we entered into a share and purchase agreement ("SPA") to acquire all of outstanding ordinary shares of Corlieve, a privately held French gene therapy company ("Corlieve Transaction"). On July 30, 2021 ("Acquisition Date"), the Company acquired Corlieve. The Company evaluated the Corlieve transaction as to whether or not the transaction should be accounted for as a business combination or asset acquisition. Refer to Note 3 "*Corlieve transaction*" for further detail.

a. Goodwill

Goodwill represents the excess of the fair value of the consideration transferred over the fair value of the net assets assumed in a business combination. Goodwill is not amortized but is evaluated for impairment on an annual basis and between annual tests if we become aware of any events occurring or changes in circumstances that would more likely than not reduce the fair value of the reporting unit below its carrying amount. As of December 31, 2022 and 2021, the Company has not recognized any impairment charges related to goodwill.

Refer to Note 3 "*Corlieve transaction*" for further detail.

b. Acquired research and development

The Company identified various licenses that combined with the results of the research and development activities conducted in relation to its target candidate for the treatment of temporal lobe epilepsy ("AMT-260") since incorporation of Corlieve in 2019 constitute an In-process research and development intangible asset ("IPR&D Intangible Asset"). The IPR&D Intangible Asset is considered to be indefinite-lived until the completion or abandonment of the associated research and development efforts and is not amortized. If and when development is completed, which generally occurs when regulatory approval to market a product is obtained, the associated asset would be deemed finite-lived and would then be amortized based on its respective useful life at that point in time. As of December 31, 2022 and 2021, the Company has not recognized any impairment charges related to the IPR&D Intangible Asset.

In case of abandonment, the IPR&D Intangible Asset will be written-off. In accordance with ASC 350, Intangibles – Goodwill and Other, the Company tests indefinite-lived intangible assets for impairment on an annual basis and between annual tests if the Company becomes aware of any events occurring or changes in circumstances that would indicate the fair value of the IPR&D Intangible Asset is below its carrying amount.

Refer to Note 3 “*Corlieve transaction*” for further detail.

c. Contingent consideration

Each reporting period, the Company revalues the contingent consideration obligations associated with the Corlieve transaction to their fair value and records changes in the fair value within research and development expenses. Changes in contingent consideration result from changes in assumptions regarding the probabilities of achieving the relevant milestones, or probability of success (“POS”), the estimated timing of achieving such milestones, and the interest rate to discount the payments. Payments made soon after the acquisition date are recorded as cash flows from financing activities, and payments, or the portion of the payments, not made soon after the acquisition date are recorded as cash flows from operating activities.

Refer to Note 3 “*Corlieve transaction*” for further detail.

2.3.6 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.

2.3.7 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.

2.3.8 Net (loss) / income per share

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

Diluted net (loss) / income per share reflects the dilution that would occur if share options or warrants to issue ordinary shares were exercised, performance or restricted share units were distributed, or shares under the employee share purchase plan were issued. However, potential ordinary shares are excluded if their effect is anti-dilutive.

Refer to Note 18 “*Basic and diluted earnings per share*” for further information.

2.3.9 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, Property, Plant, and Equipment*. 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.

Refer to Note 2.3.5 "*Corlieve transaction*" for information on impairment testing related to goodwill and acquired research and development intangible assets.

2.3.10 Investment securities

Investment securities consist of sovereign debt with residual maturities of less than 12 months (presented as current) and beyond (presented as non-current). The Company classifies these securities as held-to-maturity. Held-to-maturity securities are those securities in which the Company has the ability and intent to hold the security until maturity. Held-to-maturity securities are recorded at amortized cost, adjusted for the amortization or accretion of premiums or discounts. Premiums and discounts are amortized or accreted over the term of the related held-to-maturity security as an adjustment to yield using the effective interest rate method.

Investments securities with original maturities of less than three months when purchased are presented within cash and cash equivalents (December 13, 2022: \$21.2 million, December 31, 2021: nil).

A decline in the market value of any investment security below cost that is deemed to be other than temporary results in a reduction in the carrying amount to fair value. The impairment is charged to operations and a new cost base for the security is established. Other-than-temporary impairment charges are included in interest and other income (expense), net. Interest income is recognized when earned.

Refer to Note 5 "*Investment securities*" for further information.

2.3.11 Accounts receivable

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

2.3.12 Inventories

The Company started producing commercial materials in April 2022 to supply CSL Behring with the Product in accordance with the June 2020 Development and Commercial Supply Agreement between the Company and CSL Behring. From this date onwards, the Company presents the costs associated with the aforementioned activities as cost of contract manufacturing. Refer to Note 4, "*Collaboration arrangements and concentration of credit risk*" for further detail.

Per ASC 330, Inventory, inventory is stated at the lower of cost or estimated net realizable value, on a first-in, first-out basis. The Company capitalizes raw materials to the extent these can be used in the manufacturing of the Product. The Company uses standard costs, approximating average costs to determine its cost basis for work in progress and finished goods. The Company's assessment of recoverability value requires the use of estimates regarding the net realizable value of its inventory balances, including an assessment of excess or obsolete inventory. As applicable, write-downs resulting from adjustments to net realizable value will be recorded to cost of contract manufacturing.

2.3.13 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.

2.3.14 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 current assets or as non-current assets based on the timing of the right to consideration.

2.3.15 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

2.3.16 Leases

The Company records leases in accordance with *ASC 842, Leases* and determines if an arrangement is a lease at inception. Operating lease right-of-use assets and lease liabilities are initially recognized based on the present value of future minimum lease payments over the lease term at commencement date calculated using an incremental borrowing rate applicable to the lease asset, unless the implicit rate is readily available. Lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. Leases with a term of twelve months or less are not recognized on the consolidated balance sheets.

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 within cash flows from operations within the Consolidated statements of cash flows.

2.3.17 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, if any, are presented in accrued expenses.

2.3.18 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.

2.3.19 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.

In 2016, the Company adopted a qualified 401(k) Plan for all employees located in the United States. The 401(k) Plan offers both a pre-tax and post-tax (Roth) component. Employees may contribute up to the IRS statutory limit 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.

2.3.20 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. Compensation expense related to Performance Share Units is recognized when the Company considers achievement of the milestones to be probable. 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.

2.3.21 Revenue recognition

The Company primarily generates revenue from its commercialization and license agreement with CSL Behring and its collaboration, research, and license agreements with BMS for the development and commercialization of product candidates.

CSL Behring collaboration

On June 24, 2020 ("Signing Date"), the Company entered into a commercialization and license agreement pursuant to which CSL Behring received exclusive global rights to etranacogene dezaparvovec ("Product"). The Company concluded that CSL Behring is a customer in accordance with *ASC 606, Revenue from Contracts with Customers* and identified two material performance obligations related to the CSL Behring Agreement:

- (i) Sale of the exclusive global rights to etranacogene dezaparvovec, our investigational gene therapy for patients with hemophilia B (the "Product") ("License Sale"); and

- (ii) Generate information to support the regulatory approval of the current and next generation manufacturing process of the Product and to provide any such information generated to CSL Behring (“Manufacturing Development”).

These performance obligations are considered distinct from one another, as CSL Behring can benefit from the identified service either on its own or together with other resources that are readily available to CSL Behring, and as the performance obligations are separately identifiable from other performance obligations in the CSL Behring Agreement.

Refer to Note 4 “*Collaboration arrangements and concentration of credit risk*” for further detail.

Bristol-Myers Squibb collaboration

The Company initially entered into collaboration, research, and license agreements with Bristol-Myers Squibb (“BMS”) in 2015 (“BMS CLA”) and amended them in 2020 (“amended BMS CLA”). The agreement terminated on February 21, 2023 (“Termination Date”).

The Company evaluated the initial BMS CLA and determined that its performance obligations were as follows as of the amended BMS CLA:

- 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 4, “*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.

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 4, “*Collaboration arrangements and concentration of credit risk*”, for a detailed discussion).

Collaboration and Manufacturing Revenue

The Company recognized Collaboration Revenue associated with optional work orders it received from BMS to provide analytical development and process development activities that were reimbursable by BMS in accordance with the BMS CLA as well as the amended BMS CLA.

2.3.22 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 employee retention credits received under the U.S. Coronavirus Aid, Relief, and Economic Security Act, income related to a settlement agreement that the Company and VectorY B.V. entered into in April 2021, as well as income from subleasing part of the Company’s Amsterdam facility. Other expense consists of expenses incurred in relation to the subleasing income.

2.3.23 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.

2.3.24 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, 2022, and 2021, the Company did not have any significant unrecognized tax benefits.

2.3.25 Recently Adopted Accounting Pronouncements

ASU 2021-10: Government Assistance

In November 2018, the FASB issued ASU 2021-10, Government Assistance (Topic 832) which discussed the requirements for disclosures, to be applied prospectively or retrospectively, related to transactions with a government. ASU 2021-10 is effective for fiscal years beginning after December 15, 2021. The new disclosure requirements required disclosures around 1) information about the nature of the transactions and the related accounting policy used to account for the transactions, 2) the line items on the balance sheet and income statement that are affected by the transactions, and the amounts applicable to each financial statement line item, and 3) significant terms and conditions of the transactions, including commitments and contingencies. The Company currently includes information on government grants and the adoption of ASU 2021-10 on January 1, 2022 has not had a material impact on the Company's consolidated financial statements.

Recent Accounting Pronouncements Not Yet Effective

None.

3. Corlieve transaction

At the Acquisition Date, the Company acquired Corlieve. Following Corlieve's formation in November 2019, Corlieve obtained exclusive licenses to certain patents from two French research institutions that continue to collaborate with the Company. Corlieve also obtained an exclusive license from Regenxbio Inc. ("Regenxbio") to use AAV9 to deliver any sequence that affects the expression of the Glutamate inotropic receptor kainate type subunit 2 ("GRIK2") gene sequence in humans. Corlieve and Regenxbio simultaneously entered into a collaboration plan related to agreed joint preclinical research and development activities. At the Acquisition Date, Corlieve and its Swiss subsidiary, Corlieve Therapeutics AG, employed seven employees. Corlieve's result for the full year 2021 was a \$7.3 million loss of which \$4.1 million was included in the Company's consolidated results.

The Company evaluated the Corlieve transaction as to whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen test to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. Based on the fair values of the gross assets acquired, the Company determined the screen test was not met. The Company further analyzed whether or not the acquired inputs and processes that have the ability to create outputs would meet the definition of a business. Significant judgment is required in the application of the screen test to determine whether an acquisition is a business combination or an acquisition of assets.

Identifiable assets and liabilities of Corlieve, including identifiable intangible assets, were recorded at their fair values as of the Acquisition Date, when the Company obtained control. The excess of the fair value of the consideration transferred over the fair value of the net assets acquired was recorded as goodwill.

Consideration

On the Acquisition Date, the Company acquired 97.7% of the outstanding ordinary shares of Corlieve in return for EUR 44.9 million (\$53.3 million as of the Acquisition Date). The Company financed the Corlieve Transaction from its cash on hand. The Company acquired the remaining outstanding ordinary shares in February, July and September 2022 for a total of EUR 1.8 million (\$1.9 million).

In addition to the payments to acquire 100% of the outstanding ordinary shares, Corlieve's former shareholders are eligible to receive up to EUR 40.0 million (\$42.8 million as of December 31, 2022) upon achievement of certain development milestones through Phase I/II and EUR 160.0 million (\$171.3 million as of December 31, 2022) upon achievement of certain milestones associated with Phase III development and obtaining approval to commercialize Corlieve's target candidate for the treatment of temporal lobe epilepsy ("AMT-260" or "TLE") in the United States of America and the European Union. The Company may elect to pay up to 25% of such milestone payments through the issuance of the Company's ordinary shares.

As of the Acquisition Date, the Company recorded EUR 20.2 million (\$24.0 million) as a contingent liability (presented as "Non-current liability") for the fair value of these milestone payments.

Identified intangible assets

The Company identified various licenses that combined with the results of the research and development activities conducted in relation to AMT-260 since incorporation of Corlieve in 2019 constitute an IPR&D Intangible Asset.

The Company determined the fair value of the IPR&D Intangible Asset using a present value model based on expected cash flows. Estimating the amounts and timing of cash flows required to complete the development of AMT-260 as well as net sales, cost of goods sold, and sales and marketing costs involved considerable judgment and uncertainty. The expected cash flows are materially impacted by the probability of successfully completing the various stages of development (i.e., dosing of first patient in clinical trial, advancing into late-stage clinical development and obtaining approval to commercialize a product candidate) as well as the weighted average cost of capital of 10.4% used to discount the expected cash flows. Based on all such information and its judgment the Company estimated the fair value of the IPR&D Intangible Asset at EUR 53.6 million (\$63.6 million) as of the Acquisition Date.

Deferred tax liability, net

Corlieve's deferred tax assets at the time of acquisition amounted to EUR 1.5 million (\$1.7 million). Recognition of the IPR&D Intangible Asset gave rise to a deferred tax liability of EUR 13.4 million (\$15.9 million) at the enacted French corporate income tax rate of 25.0%. The Company consequently recorded a net deferred tax liability of EUR 11.9 million (\$14.2 million as of the Acquisition Date). Changes in the net deferred tax liability after the Acquisition Date will be recorded in income tax expense in the consolidated statements of operations.

Goodwill

Goodwill represents the excess of total consideration over the estimated fair value of net assets acquired. The Company recorded EUR 23.9 million (\$28.4 million) of goodwill in the consolidated balance sheet as of the Acquisition Date. The goodwill primarily relates to the recognition of a deferred tax liability recognized in association with the IPR&D Intangible asset of EUR 13.4 million (\$15.9 million as of Acquisition Date) as well as the fair market value of the experienced workforce and potential synergies from the acquisition. The Company allocated the goodwill to its reporting unit. The Company does not expect any portion of this goodwill to be deductible for income tax purposes.

Debt

As of the Acquisition Date, Corlieve held a loan with outstanding amount equal to EUR 1.0 million (\$1.2 million), which loan was repaid in its entirety in September 2021. As of the Acquisition Date, Corlieve also held a loan with outstanding amount equal to EUR 0.4 million (\$0.4 million), which was repaid in its entirety in December 2021.

Other

As of the Acquisition Date, the Company also acquired other assets and assumed other liabilities, which included among others, EUR 2.9 million (\$3.4 million) of current assets, which consisted of EUR 2.8 million (\$3.3 million) of cash, and EUR 1.1 million (\$1.3 million) of current liabilities.

4. Collaboration arrangements and concentration of credit risk

CSL Behring collaboration

On the Signing Date, 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 received exclusive global rights to the Product. On May 6, 2021, a day after the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, the CSL Behring Agreement became fully effective ("Closing").

The Company concluded that CSL Behring is a customer in accordance with Topic 606.

The Company identified two material performance obligations related to the CSL Behring Agreement:

- (i) License Sale; and
- (ii) Manufacturing Development.

These performance obligations are considered distinct from one another, as CSL Behring can benefit from the identified service either on its own or together with other resources that are readily available to CSL Behring, and as the performance obligations are separately identifiable from other performance obligations in the CSL Behring Agreement. The Company continued to develop the Product between the Signing Date and Closing and performed certain reimbursable activities to fulfill the transfer of the global rights ("Additional Covenants" and together with the License the "License Sale"). The Additional Covenants are not considered distinct from the performance obligation to sell the license to CSL Behring as CSL Behring could not benefit from the Additional Covenants on their own, or have these activities be performed with readily available resources.

License Sale

The Company determined that the fixed upfront payment of \$450.0 million and the \$12.4 million that the Company received in May 2021 in relation to the Additional Covenants should be allocated to the License Sale. In addition, the Company concluded that variable milestone payments, sales milestone payments and royalties should be allocated to the License Sale performance obligation as well. The Company determined that the License Sale was completed on May 6, 2021, when it transferred the license and CSL Behring assumed full responsibility for the development and commercialization of the Product. At Closing, the Company evaluated the amounts of potential payments and the likelihood that the payments will be received. The Company utilized the most likely amount method to estimate the variable consideration to be included in the transaction price. Since the Company cannot control the achievement of regulatory and first commercial sales milestones, the Company concluded that the potential payments were constrained as of Closing. The Company determined that it would recognize revenue related to these payments only to the extent that it becomes probable that no significant reversal of recognized cumulative revenue will occur thereafter.

The Company determined that achievement of a total of \$55.0 million of milestone payments related to the submissions of a biologics license application (“BLA”) and market authorization application (“MAA”) was probable as of February 25, 2022, the time of filing the 2021 financial statements, and hence recorded these as license revenue in the year ended December 31, 2021. In March and April 2022, the global regulatory submissions were submitted and the Company received the \$55.0 million owed to it from CSL Behring.

The Company recorded \$100.0 million in variable milestone revenue related to a first sale of HEMGENIX™ in the U.S. during the year ended December 31, 2022 as the Company considers the occurrence of this event to be probable following the November 2022 BLA approval of HEMGENIX™. Despite the approval of the MAA for HEMGENIX™ by the European Medicines Agency (“EMA”) in February 2023, the Company did not record the \$75.0 million variable milestone payment related to a first sale of HEMGENIX™ in the one of five major European countries, namely France, Germany, Italy, Spain, and the United Kingdom, as license revenue in the year ended December 31, 2022. The Company considers that the milestone is only owed if achieved prior to July 2, 2023, which is contingent on factors outside the Company’s control and thus the Company determined that occurrence was not probable as of December 31, 2022.

The Company is also eligible to receive up to \$1.3 billion in additional payments based on the achievement of 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. The Company will include payments related to sales milestones in the transaction price when their achievement becomes probable, and it will include royalties on the sale of Product once these have been earned.

The Company recognized \$100.0 million and \$517.4 million of revenues related to the License Sale in the years ended December 31, 2022 and December 31, 2021, respectively (nil in 2020).

The Company records expenses related to its existing license and other agreements as well as its financial advisor for a high single digit percentage of any such revenue recognized associated to meeting a milestone.

Manufacturing Development

The Company determined that the \$50.0 million variable milestone payment related to Manufacturing Development should be allocated to the Manufacturing Development performance obligation. The Company concluded that this milestone payment represents the stand-alone selling price (“SSP”) of the services based on the estimated cost of providing the services including a reasonable margin. Manufacturing Development includes providing information regarding a next generation manufacturing process of the Product to CSL Behring. CSL Behring did not request such services during the year ended December 31, 2022.

The variable consideration will be reduced if the Company does not complete the development by pre-agreed dates following BLA, respectively MAA approval. The Company utilized the most likely amount method to estimate the variable consideration to be included in the transaction price. As of December 31, 2022, the Company has not recognized any revenue related to the Manufacturing Development milestone.

Contract manufacturing

On the Signing Date, 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 commensurate with the SSP. The Company will be responsible for supplying development and commercial Product until such time that these capabilities may be transferred to CSL Behring or a designated contract manufacturing organization. On September 6, 2022, CSL Behring notified the Company of its intent to transfer manufacturing technology related to the Product in the coming years to a third-party contract manufacturer designated by CSL Behring. CSL Behring also requested that the Company continue to serve as a manufacturer of the Product after the Company completes the technology transfer to a third party. The Company and CSL Behring are in the process of negotiating the terms of the transfer of manufacturing responsibility pursuant to the CSL Behring Agreement.

The Company generated \$1.7 million contract manufacturing revenue from sales to CSL Behring. The Company recognizes contract manufacturing revenue when CSL Behring obtains control of the Product. The Company incurred \$2.1 million of cost in relation to its contract manufacturing activities during the year ended December 31, 2022.

Collaboration services

Following Closing, the Company was facilitating the completion of the HOPE-B clinical trial on behalf of CSL Behring until CSL Behring took over the execution of the clinical trials in December 2022. Activities related to on-demand development services as well as activities related to the completing the HOPE-B clinical trial are reimbursed by CSL Behring at an agreed full-time-employee rate (“FTE-rate”) and CSL Behring also reimburses agreed third-party expenses incurred in relation to performing these activities. The Company concluded that these rights at Closing do not represent material rights.

The Company recognized \$3.0 million of collaboration revenue in the year ended December 31, 2022, compared to \$2.4 million and nil in the same periods in 2021 and 2020.

Accounts receivable and contract asset

As of December 31, 2022, the Company recorded accounts receivable of \$2.2 million from CSL Behring related to collaboration services as well as a contract asset of \$100.0 million expected to be received from CSL Behring following the first sale of HEMGENIX™ in the U.S in 2023.

As of December 31, 2021, the Company recorded accounts receivable of \$2.9 million from CSL Behring related to collaboration services as well as a contract asset of \$55.0 million associated with milestone payments due upon CSL Behring’s global regulatory submissions for HEMGENIX™.

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.

2020 amendment

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

Since the December 2020 amendment, BMS no longer was entitled to designate a fifth to tenth Collaboration Targets and as such the Company's remaining obligations under the amended BMS CLA were substantially reduced. The Company also no longer was 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 were being advanced, BMS might have placed a purchase order to be supplied with research, clinical and commercial supplies.

The amended BMS CLA did not extend the initial four-year research term that expired in May 2019. BMS could place purchase orders to be provided with limited services primarily related to analytical and development efforts in respect of the four Collaboration Targets. BMS could have requested such services for a period not to exceed the earlier of (i) the completion of all activities under a Research Plan and (ii) November 30, 2023. BMS continued to reimburse the Company for these services.

2022 Termination

On November 21, 2022, the Company received written notice that BMS is terminating the BMS CLA as amended effective February 21, 2023.

Services to BMS were rendered by the Dutch operating entity. Total collaboration and license revenue generated with BMS are as follows (presented as revenue from a related party up until the effective date of the amended BMS CLA and presented as revenue after the effective date):

	Years ended December 31,		
	2022	2021 (in thousands)	2020
Bristol Myers Squibb	\$ 1,752	\$ 4,176	\$ 37,514
	<u>\$ 1,752</u>	<u>\$ 4,176</u>	<u>\$ 37,514</u>

Amounts owed by BMS in relation to the Collaboration and License Revenue are as follows (presented as "Accounts receivables" as of December 31, 2022 and 2021):

	December 31, 2022	December 31, 2021
	(in thousands)	
Bristol Myers Squibb	\$ 136	\$ 914
Total	<u>\$ 136</u>	<u>\$ 914</u>

License Revenue

The Company recognized no License Revenue for the year ended December 31, 2022 (December 31, 2021: nil million, December 31, 2020: \$33.0 million).

In 2015 the Company received \$75.1 million of payments that it allocated to License Revenue. 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.

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 had on its measure of progress towards the completion of its performance obligation related to License Revenue and determined that its remaining performance obligation under the amended BMS CLA was immaterial and 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 included variable consideration related to any research, development, and regulatory milestone payments, in the transaction price once it considered it 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 with the exception of a \$4.4 million research milestone payment received and recorded as License Revenue in December 2020 did not consider this probable as of December 31, 2021. No variable consideration became due prior to the termination of the amended BMS CLA on February 21, 2023.

Under the amended BMS CLA, the Company would have recognized License Revenue related to product sales by BMS from any of the Collaboration Targets when the sales would have occurred. The Company was eligible to receive net sales-based milestone payments and tiered mid-single to low double-digit royalties on product sales.

Collaboration Revenue

The Company recognized collaboration revenues associated with Collaboration Target-specific pre-clinical analytical development and process development activities that were 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 was recognized when performance obligations were satisfied.

The Company generated \$1.8 million collaboration revenue for the year ended December 31, 2022 (December 31, 2021: \$4.2 million; December 31, 2020: \$0.2 million).

5. Investment securities

The following table summarizes the Company's investments into sovereign debt as of December 31, 2022:

	At December 31, 2022			Estimated fair value
	Amortized cost, as adjusted	Gross unrealized holding gains	Gross unrealized holding losses	
(in thousands)				
Current investments:				
Obligations of governmental agencies (held-to-maturity)	\$ 124,831	\$ —	\$ (283)	\$ 124,548
Non-current investments:				
Obligations of governmental agencies (held-to-maturity)	39,984	—	(43)	39,941
Total	\$ 164,815	\$ —	\$ (326)	\$ 164,489

No investments classified as held-to-maturity were purchased in the prior years. Inputs to the fair value of the investments are considered Level 2 inputs.

6. Inventories

The following table summarizes the inventory balances as of December 31, 2022:

	December 31, 2022	December 31, 2021
	(in thousands)	
Raw materials	\$ 3,584	\$ —
Work in progress	1,874	—
Finished goods	1,466	—
Inventories	\$ 6,924	\$ —

7. Fair value measurement and Other non-operating (losses) / gains

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 licensing and collaboration partners, 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 material financial assets include cash and cash equivalents, restricted cash and investment securities. Cash and cash equivalents and restricted cash are measured at fair value using Level 1 inputs. Restricted cash is included within "Other non-current assets" within the consolidated balance sheets. Investment securities are measured at amortized cost.

The following table sets forth the balances and changes in fair values of liabilities that are measured at fair value using Level 3 inputs:

	Contingent consideration	Derivative financial instruments (in thousands)	Total
Balance at December 31, 2019	\$ —	\$ 3,075	\$ 3,075
Net gains recognized in profit or loss	—	(2,300)	(2,300)
Derecognition of BMS 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
Amount recorded for contingent consideration on Acquisition Date of Corlieve	23,950	—	23,950
Net losses recognized in profit or loss	6,683	160	6,843
Currency translation effects	(1,091)	—	(1,091)
Balance at December 31, 2021	\$ 29,542	\$ 2,805	\$ 32,347
Net losses recognized in profit or loss	7,080	(2,760)	4,320
Currency translation effects	(1,306)	(45)	(1,351)
Balance at December 31, 2022	\$ 35,316	\$ —	\$ 35,316

Contingent consideration

The Company is required to pay up to EUR 178.8 million (\$191.4 million at the December 31, 2022 foreign exchange rate) to the former shareholders of Corlieve upon the achievement of contractually defined milestones in connection with the Company’s acquisition of Corlieve (refer to Note 3 “*Corlieve transaction*”). The Company recorded a liability for the fair market value of the contingent consideration of EUR 20.2 million (\$24.0 million) at the Acquisition Date. The fair market value was determined using unobservable initial inputs with respect to (i) the probability of achieving the relevant milestones, or POS, (ii) the estimated timing of achieving such milestones, and (iii) the interest rate used to discount the payments. The Company determined the fair market value of the contingent consideration by calculating the probability-adjusted payments based on each milestone’s probability of achievement. The probability-adjusted payments were then discounted to present value using a discount rate representing the Company’s credit risk. This discount rate was determined using the effective interest rate of the Company’s existing debt facility adjusted for difference in maturity dates based on market data on effective yields for U.S. bonds with a CCC credit rating.

The fair value of the contingent consideration as of December 31, 2022 was \$35.3 million (2021: \$29.5 million) using discount rates ranging from 14.0% to 14.4% (December 31, 2021: 10.9% to 11.9%) as well as a 66.0% (December 31, 2021: 55.0%) likelihood of AMT-260 advancing into clinical development by no later than late 2023. If as of December 31, 2022 the Company had assumed a 100% likelihood of AMT-260 advancing into clinical development, then the fair value of the contingent consideration would have increased to \$48.8 million. If as of December 31, 2022 the Company assumed that it would discontinue development of the AMT-260 program, then the contingent consideration would be released to income. Changes in fair value of the contingent liability are recognized within research and development expenses in the consolidated statements of operations.

As of December 31, 2022, the Company classified \$26.0 million of the total contingent consideration of \$35.3 million as current liabilities. The balance sheet classification between current and non-current liabilities is based upon the Company’s best estimate of the timing of settlement of the remaining relevant milestones.

Derivative financial instruments

The Company recorded the following results in other non-operating (losses) / gains related to the changes in the fair value of derivative financial instruments.

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
Other non-operating gains:			
Derivative gains	\$ 2,760	\$ —	\$ 483
Total other non-operating gains:	2,760	—	483
Other non-operating losses:			
Derivative losses	—	(160)	—
Other non-operating (losses) / gains, net	\$ 2,760	\$ (160)	\$ 483

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. During the year ended December 31, 2020, the Company recognized a \$3.1 million gain in non-operating (losses) / gains related to the fair value changes of the BMS warrants, which includes \$0.8 million from the derecognition of the BMS warrants on December 1, 2020.

On December 1, 2020, as part of the amended BMS CLA, the Company and BMS 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, the Company (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 determined that the CoC-payment should be recorded as a derivative financial liability as of the December 1, 2020 initial recognition 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 the 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 transaction within the biotechnology industry. The Company estimated this unobservable input using the best information available as of December 2021. 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 judgment 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 31, 2021 was \$2.8 million. The Company recorded a \$0.2 million loss in the year ended December 31, 2021 related to an increase in the fair market value of the derivative financial liability and a \$2.6 million loss in the year ended December 31, 2020 related to the initial recognition of this derivative financial liability

The Company determined the fair market value of the derivative financial liability to be nil as of December 31, 2022 as no change of control transaction had been consummated prior to the termination of the amended BMS CLA on February 21, 2023. The Company considered the probability of a change of control transaction occurring before the Termination Date to be remote. This resulted in the derecognition of the derivative financial liability for the year ended December 31, 2022.

Accordingly, the Company recorded a \$2.8 million gain within "Other non-operating (losses) / gains" in the year ended December 31, 2022

Other

As of December 31, 2022, the Company recorded \$0.3 million liability related to consideration for post-acquisition services, presented within Other non-current liabilities in connection with the Company's acquisition of Corlieve (December 31, 2021: \$0.8 million).

Investment securities

Refer to Note 5 "Investment securities" for the fair value of the investment securities as of December 31, 2022.

8. Property, plant, and equipment, net

The following table presents the Company's property, plant, and equipment as of December 31:

	December 31, 2022	December 31, 2021
	(in thousands)	
Leasehold improvements	\$ 44,871	\$ 45,372
Laboratory equipment	39,393	25,499
Office equipment	4,985	4,465
Construction-in-progress	5,409	5,069
Total property, plant, and equipment	94,658	80,405
Less accumulated depreciation	(44,126)	(36,900)
Property, plant and equipment, net	\$ 50,532	\$ 43,505

Total depreciation expense was \$8.2 million for the year ended December 31, 2022 (December 31, 2021: \$6.1 million, December 31, 2020: \$5.7 million). Depreciation expense is allocated to research and development expenses and cost of contract manufacturing 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, 2022	December 31, 2021
	(in thousands)	
Lexington, Massachusetts (United States of America)	\$ 20,258	\$ 17,311
Amsterdam (the Netherlands)	30,252	26,160
Other	22	34
Total	\$ 50,532	\$ 43,505

9. Right-of-use asset and lease liabilities

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.

In December 2021, the Company entered into a new lease for an additional facility in Lexington, Massachusetts, United States of approximately 13,501 square feet of space. The lease commenced in May 2022, is set for seven years and is non-cancellable. The lease is renewable for one five-year term.

In February 2022, the Company also entered into a new lease for an additional facility in Lexington, Massachusetts, United States of approximately 12,716 square feet. The lease commenced in November 2022 and is set for a non-cancellable period of seven years and four months. The lease is renewable for one five-year term.

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 lease for the 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 \$4.8 million (EUR 4.5 million) as of December 31, 2022.

In May 2021, the Company entered into a sublease agreement to let an additional approximately 1,080 square meters of office space to accommodate the hiring of additional full-time employees. The lease expires in October 2028 and includes an option to break the lease on October 31, 2023.

Operating lease liabilities

The components of lease cost were as follows:

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Operating lease cost	\$ 5,932	\$ 5,306	\$ 5,052
Variable lease cost	785	698	607
Sublease income	(849)	(907)	(904)
Total lease cost	\$ 5,868	\$ 5,097	\$ 4,755

The table below presents the lease-related assets and liabilities recorded on the Consolidated balance sheets.

	December 31,	December 31,
	2022	2021
	(in thousands)	
Assets		
Operating lease right-of-use assets	\$ 32,726	25,573
Liabilities		
Current		
Current operating lease liabilities	8,382	5,774
Non-current		
Non-current operating lease liabilities	31,719	28,987
Total lease liabilities	\$ 40,101	34,761

Other information

The weighted-average remaining lease term as of December 31, 2022, is 7.2 years, compared to 8.3 years as of December 31, 2021, and the weighted-average discount rate as of December 31, 2022 is 11.2%, compared to 11.3% as of December 31, 2021. The Company uses an incremental borrowing rate applicable to the lease asset.

The table below presents supplemental cash flow and non-cash information related to leases.

	Year ended December 31,		
	2022	2021	2020
	(in thousands)		
Cash paid for amounts included in the measurement of lease liabilities			
Operating cash flows for operating leases	\$ 7,532	\$ 5,738	\$ 5,769
Right-of-use asset obtained in exchange for lease obligation			
Operating lease	\$ 9,824	\$ 1,699	\$ —

Undiscounted cash flows

The table below reconciles the undiscounted cash flows as of December 31, 2022, 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, 2022.

	Lexington	Amsterdam ⁽¹⁾	Other	Total
	(in thousands)			
2023	\$ 5,236	\$ 3,042	\$ 104	\$ 8,382
2024	5,504	1,993	104	7,601
2025	5,859	1,993	104	7,956
2026	6,031	1,993	104	8,128
2027	6,207	1,997	104	8,308
Thereafter	9,343	7,190	469	17,002
Total lease payments	\$ 38,180	\$ 18,208	\$ 989	\$ 57,377
Less: amount of lease payments representing interest payments	(10,611)	(6,268)	(397)	(17,276)
Present value of lease payments	27,569	11,940	592	40,101
Less: current operating lease liabilities	(5,236)	(3,042)	(104)	(8,382)
Non-current operating lease liabilities	\$ 22,333	\$ 8,898	\$ 488	\$ 31,719

(1) Payments are due in EUR and have been translated at the foreign exchange rate as of December 31, 2022, of \$1.07 / €1.00

10. Intangible assets, net and Goodwill

The following table presents the Company's acquired licenses and acquired IPR&D as of December 31:

	December 31, 2022	December 31, 2021
	(in thousands)	
Acquired licenses	\$ 2,346	\$ 4,755
Less accumulated amortization	(900)	(2,827)
Acquired licenses, net	\$ 1,446	\$ 1,928
Acquired IPR&D Intangible Asset	57,332	60,758
Intangibles, net	\$ 58,778	\$ 62,686

a. Acquired licenses

All acquired licenses are owned by uniQure biopharma B.V, a subsidiary of the Company. The remaining weighted average life is 11.5 years as of December 31, 2022. (December 31, 2021 10.8 years.)

As of December 31, 2022, the estimated future amortization expense for each of the five succeeding years and the period thereafter is as follows:

Years	Amount (in thousands)
2023	\$ 126
2024	126
2025	126
2026	126
2027	126
Thereafter	816
Total	\$ 1,446

The amortization expense related to licenses for the year ended December 31, 2022 was \$0.4 million (December 31, 2021: \$1.2 million; December 31, 2020: \$4.6 million). In 2020, the Company disposed of a number of licenses determined to have no alternative future use. The impairment expense related to licenses for the year ended December 31, 2022 was \$0.0 million (December 31, 2021: \$0.0 million; December 31, 2020 \$0.3 million).

b. Acquired in-process research and development

As part of its acquisition of Corlieve as of July 30, 2021, the Company identified certain intangible assets related to an IPR&D Intangible Asset. Refer to Note 3 “*Corlieve transaction*”.

c. Goodwill

As part of its acquisition of Corlieve as of July 30, 2021, the Company recorded goodwill. Refer to Note 3 “*Corlieve transaction*”.

11. Accrued expenses and other current liabilities

Accrued expenses and other current liabilities include the following items:

	December 31, 2022	December 31, 2021
	(in thousands)	
Accruals for goods received from and services provided by vendors-not yet billed	\$ 11,120	\$ 13,012
Personnel related accruals and liabilities	17,201	12,603
Accrued contract fulfillment costs and costs to obtain a contract	2,250	2,872
Total	\$ 30,571	\$ 28,487

12. Long-term debt

On June 14, 2013, the Company entered into a venture debt loan facility with Hercules Capital, Inc. (formerly known as Hercules Technology Growth Capital, Inc.) (“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 that both refinanced the then-existing \$20.0 million 2016 Amended Facility and allowed the Company to draw down an additional \$15.0 million (“2018 Amended Facility”). The 2018 Amended Facility extended the loan’s maturity date from May 1, 2020 until June 1, 2023. The interest rate was adjustable and was the greater of (i) 8.85% and (ii) 8.85% plus the prime rate less 5.50% per annum. In May 2020 the Company paid a back-end fee of \$1.0 million in relation to the 2016 Amended Facility.

On January 29, 2021, the Company and Hercules amended the 2018 Amended Facility (“2021 Amended Facility”). Pursuant to the 2021 Amended Facility, Hercules agreed to an additional Facility of \$100.0 million (“Tranche B”) increasing the aggregate principal amount of the term loan facilities from \$35.0 million to up to \$135.0 million. On January 29, 2021, the Company drew down \$35.0 million of the Tranche B. Advances under Tranche B bore 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 of \$70.0 million and all accrued but unpaid interest on advances under Tranche B was due on June 1, 2023, which date could have been extended by the Company by up to two twelve-month periods. Advances under the 2021 Amended Facility could have been prepaid without charge after July 29, 2021. The back-end fee in respect of advances under the 2021 Amended Facility ranged from 1.65% to 6.85%, depending on the repayment date. In addition to Tranche B, the 2021 Amended Facility had also extended the interest only payment period of the previously funded \$35.0 million term loan (“Tranche A”) from January 1, 2022 to June 1, 2023.

On December 15, 2021, the Company and Hercules amended and restated the 2021 Amended Facility (“2021 Restated Facility”). Pursuant to the 2021 Restated Facility, Tranche A and Tranche B of the 2021 Amended Facility with a total outstanding balance of \$70.0 million were consolidated into one tranche with a total commitment of \$100.0 million. The Company drew down an additional \$30.0 million, resulting in total principal outstanding as of December 31, 2021 of \$100.0 million. The 2021 Restated Facility extended the loan’s maturity date from June 1, 2023 until December 1, 2025. The interest-only period was extended from January 1, 2023 to December 1, 2024, or December 1, 2025 if, prior to June 30, 2024, either (a) the BLA for AMT-061 is approved by the U.S. Food and Drug Administration (“FDA”) or (b) AMT-130 is advanced into a pivotal trial. On November 22, 2022, the FDA approved the BLA for AMT-061 resulting in the extension of the interest-only period to December 1, 2025. The Company is required to repay the entire principal balance on the maturity date. The interest rate is adjustable and is the greater of (i) 7.95% and (ii) 7.95% plus the prime rate less 3.25% per annum. Under the 2021 Restated Facility, the Company owes a back-end fee of \$2.5 million on June 1, 2023 and a back-end fee of \$4.85 million on the maturity date.

The amortized cost (including interest due presented as part of accrued expenses and other current liabilities) of the 2021 Restated Facility was \$103.8 million as of December 31, 2022, compared to an amortized cost of \$101.6 million for the 2021 Restated Facility as of December 31, 2021, and is recorded net of discount and debt issuance costs. The foreign currency loss on the loan was \$5.8 million in 2022 (2021: loss of \$5.3 million; 2020: gain of \$3.1 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:

<u>Years</u>	<u>Amount</u> <u>(in millions)</u>
2022	\$ 11.5
2021	7.2
2020	3.7

As a covenant in the 2021 Restated 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. Following the approval of the BLA by the FDA for AMT-061 in November 2022, the Company, beginning on April 1, 2024, is required to keep a minimum of unrestricted cash of at least 30% of the loan amount outstanding. In combination with other covenants, the 2021 Restated 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 to its shareholders. The Company secured the facilities by directly or indirectly pledging its total assets of \$705.0 million with the exception of \$63.7 million of cash and cash equivalents and other current assets held by uniQure N.V and \$85.2 million of other current assets and investment held by Corlieve Therapeutics SAS.

The 2021 Restated Facility contain 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, 2022, the Company was in material compliance with all covenants and provisions.

The aggregate maturities of the loans, including \$44.5 million of coupon interest payments and financing fees, for each of the 35 months after December 31, 2022, are as follows:

<u>Years</u>	<u>Amount</u> <u>(in thousands)</u>
2023	\$ 14,870
2024	12,403
2025	117,219
Total	\$ 144,492

13. Shareholders' equity

As of December 31, 2022, the Company's authorized share capital is €4.0 million (or \$4.3 million when translated at an exchange rate as of December 31, 2022, of \$1.07 / €1.00), divided into 80,000,000 ordinary shares, each with a nominal value of €0.05. The Company's shareholders, at the 2021 Annual General Meeting of Stockholders held on June 16, 2021, approved an increase in the number of authorized ordinary shares by 20,000,000 to 80,000,000.

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, 2022, and 2021 and 2020 the Company's other comprehensive result was restricted for payment of dividends for an accumulated other comprehensive loss of \$58.3 million in 2022, an accumulated other comprehensive loss of \$28.9 million in 2021, and an accumulated other comprehensive gain of \$9.9 million in 2020.

On March 1, 2021, the Company entered into a Sales Agreement with SVB Leerink LLC ("SVB Leerink") with respect to an at-the-market ("ATM") offering program, under which the Company may, from time to time in its sole discretion, offer and sell through SVB Leerink, acting as agent, its ordinary shares, up to an aggregate offering price of \$200.0 million. The Company will pay SVB Leerink a commission equal to 3% of the gross proceeds of the sales price of all ordinary shares sold through it as sales agent under the Sales Agreement. In March and April 2021, the Company issued an aggregate of 921,730 ordinary shares at a weighted average price of \$33.52 per ordinary share, with net proceeds of \$29.6 million, after deducting underwriting discounts and net of offering expenses. The Company defers direct, incremental costs associated to this offering, except for the commission costs to SVB Leerink, which are a reduction to additional paid-in capital, and will deduct these costs from additional paid-in capital in the consolidated balance sheets proportionately to the amount of proceeds raised. During the year ended December 31, 2021, \$1.3 million of direct, incremental costs were deducted from additional paid-in capital (nil for the year ended December 31, 2022).

Following the Closing of the CSL Behring transaction, the Company consumed its tax net operating loss carryforwards from the years 2011 to 2018. The Company allocated the tax benefit from the release of the valuation allowance related to net operating loss carryforwards generated by share issuance costs incurred in 2014, 2015, 2017 and 2018 to additional paid-in capital. This resulted in an increase of additional paid-in capital of \$3.0 million in the year ended December 31, 2021.

The Company recorded \$0.8 million increase of additional paid-in capital in the year ended December 31, 2022 resulting from the release of valuation allowance for the tax benefit of share issuance costs incurred in 2018, 2019 and 2021 within the Netherlands.

14. 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,		
	2022	2021 (in thousands)	2020
Cost of manufacturing services revenue	\$ 323	\$ —	\$ —
Research and development	18,402	12,834	11,995
Selling, general and administrative	15,479	12,801	9,836
Total	\$ 34,204	\$ 25,635	\$ 21,831

Share-based compensation expense recognized by award type was as follows:

Award type/ESPP	Year ended December 31,		
	2022	2021 (in thousands)	2020
Share options	\$ 13,425	\$ 12,477	\$ 11,434
Restricted share units	15,486	11,347	7,364
Performance share units	5,267	1,783	2,990
Employee share purchase plan	26	28	43
Total	\$ 34,204	\$ 25,635	\$ 21,831

As of December 31, 2022, the unrecognized compensation cost related to unvested awards under the various share-based compensation plans were:

Award type	Unrecognized share-based compensation expense	Weighted average remaining period for recognition
	(in thousands)	(in years)
Share options	\$ 24,420	2.48
Restricted share units	24,924	1.90
Performance share units	184	0.14
Total	\$ 49,528	2.18

The Company satisfies the exercise of share options and vesting of Restricted Share Units (“RSUs”) and Performance Share Units (“PSUs”) through newly issued ordinary 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, 2022, no fully vested share options are outstanding (December 31, 2021: 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, 2018 and 2021, 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, 3,000,000 shares in 2018 and 4,000,000 shares in 2021 for a total of 12,601,471 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, 2022:

	Number of ordinary shares	Weighted average exercise price	Options	
			Weighted average remaining contractual life in years	Aggregate intrinsic value (in thousands)
Outstanding at December 31, 2021	3,308,325	\$ 31.02	7.05	\$ 8,660
Granted	1,426,966	\$ 15.90		
Forfeited	(204,224)	\$ 38.29		
Expired	(154,794)	\$ 36.86		
Exercised	(138,356)	\$ 7.81		
Outstanding at December 31, 2022	4,237,917	\$ 26.13	7.14	17,848
Thereof, fully vested and exercisable on December 31, 2022	2,139,360	\$ 28.82	5.45	8,339
Thereof, outstanding and expected to vest after December 31, 2022	2,098,557	\$ 23.38	8.86	9,509
Outstanding and expected to vest after December 31, 2021	1,521,500	\$ 38.71		

Total weighted average grant date fair value of options issued during the period (in \$ millions)		\$ 12.9
Granted to directors and officers during the period (options, grant date fair value \$ in millions)	672,908	\$ 5.9
Proceeds from option sales during the period (in \$ millions)		\$ 1.3

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, 2022	1,426,966	\$ 9.04
Granted, 2021	1,174,893	20.95
Granted, 2020	653,852	28.08
Vested, 2022	652,635	22.27
Forfeited, 2022	(204,224)	22.17

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, 2022	2,098,557	\$ 13.46
Outstanding and expected to vest, 2021	1,521,500	22.52

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:

Assumptions	Year ended December 31,		
	2022	2021	2020
Expected volatility	70%	75%	70%
Expected terms	10 years	10 years	10 years
Risk free interest rate	2.12% - 4.16%	1.21 - 1.86%	0.76% - 1.44%
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)
2022	138,356	\$ 1,848
2021	241,496	5,046
2020	498,678	11,927

Restricted Share Units

The following table summarizes the RSU activity for the year ended December 31, 2022:

	RSU	
	Number of ordinary shares	Weighted average grant-date fair value
Non-vested at December 31, 2021	710,617	\$ 38.89
Granted	1,604,533	\$ 16.10
Vested	(292,688)	\$ 39.31
Forfeited	(203,688)	\$ 23.39
Non-vested at December 31, 2022	1,818,774	\$ 20.46
Total weighted average grant date fair value of RSUs granted during the period (in \$ millions)		\$ 25.8
Granted to directors and officers during the period (shares, \$ in millions)	380,288	\$ 6.0

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
2022	1,604,533	\$ 16.10
2021	574,921	36.14
2020	376,799	48.18

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)
2022	\$ 5,104
2021	8,063
2020	12,156

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, 2022:

	PSU	
	Number of ordinary shares	Weighted average grant-date fair value
Non-vested at December 31, 2021	632,930	\$ 33.54
Granted	34,700	\$ 15.11
Vested	(213,145)	\$ 40.46
Forfeited	(53,795)	\$ 29.35
Non-vested at December 31, 2022	400,690	\$ 28.82
Total weighted average grant date fair value of PSUs granted during the period (in \$ millions)		
		\$ 0.5

The Company granted shares to certain employees in September and December 2021 and various dates during the year ended December 31, 2022 that will be earned upon achievement of defined milestones. Earned shares will vest upon the later of a minimum service period of one year or three years, or the achievement of defined milestones, subject to the grantee's continued employment. In addition, portions of the December 2021 granted to executives and other members of senior management are subject to achieving a minimum total shareholder return relative to the Nasdaq biotechnology index. The Company recognizes the compensation cost related to these grants to the extent it considers achievement of the milestones to be probable. Achievement of one of the total five defined milestones was met and one of the five defined milestones was considered probable as of December 31, 2022.

In January 2018 and January and February 2019, the Company awarded PSUs to its executives and other members of senior management. These PSUs were earned in January 2019 and January 2020, based on the Board of Directors' (the "Board") assessment of the level of achievement of agreed upon performance targets through December 31, 2018, and December 31, 2019, respectively. The PSUs awarded for the year ended December 31, 2018 vested in February 2021 and the PSUs awarded for the year ended December 31, 2019 vested in January 2022.

The following table summarizes information about the weighted average grant-date fair value of the PSUs determined as of the date those were earned for the 2019 PSUs, and the date of the grant for the 2021 and 2022 PSUs:

	Granted during the year	Weighted average grant-date fair value
2022	34,700	\$ 15.11
2021	555,600	\$ 30.19
2020	91,003	\$ 57.56

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)
2022	\$ 4,450
2021	5,074
2020	21,852

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, 2022, 11,242 shares have been issued (December 31, 2021: 4,724 and December 31, 2020: 6,181). As of December 31, 2022, a total of 116,060 ordinary shares remain available for issuance under the ESPP plan.

15. Expenses by nature

Operating expenses excluding expenses presented in other expenses included the following expenses by nature:

	Years ended December 31,		
	2022	2021 (in thousands)	2020
Employee-related expenses	\$ 119,903	\$ 96,161	\$ 75,926
Laboratory and development expenses	65,964	36,014	35,977
Office and housing expenses	17,612	14,638	13,388
Legal and advisory expenses	15,782	24,767	17,370
Other operating expenses	8,510	10,528	8,772
Patent and license expenses	9,548	3,748	2,899
Depreciation and amortization expenses	8,250	7,299	10,648
Fair value loss - Corlieve contingent consideration	7,081	6,683	-
Total	\$ 252,650	\$ 199,838	\$ 164,980

Details of employee-related expenses for the years ended December 31 are as follows:

	Years ended December 31,		
	2022	2021 (in thousands)	2020
Wages and salaries	\$ 63,704	\$ 53,078	\$ 40,919
Share-based compensation expenses	33,881	25,635	21,831
Social security costs	5,179	4,496	4,068
Health insurance	4,148	3,161	2,271
Contractor expenses	3,959	3,170	2,423
Other employee expenses	6,365	4,570	2,635
Pension costs - defined contribution plans	2,667	2,051	1,779
Total	\$ 119,903	\$ 96,161	\$ 75,926

16. Other income

Other income during the year ended December 31, 2022 was \$7.2 million compared to \$12.3 million and \$3.3 million during the same periods in 2021 and 2020, respectively.

Other income in 2022, 2021 and 2020 includes income from payments received from European authorities to subsidize the Company’s research and development efforts in the Netherlands. The amount recognized in the year ended December 31, 2022 was \$5.6 million compared to \$5.3 million in 2021 and \$1.9 million in 2020.

In addition, other income included \$2.6 million of employee retention credits received under the U.S. Coronavirus Aid, Relief, and Economic Security Act, during the year ended December 31, 2021. No such income was received in the years ended December 31, 2022 or December 31, 2020.

An additional \$3.0 million of other income was recorded in the year ended December 31, 2021, related to the receipt by the Company of 69,899 shares of VectorY B.V. in conjunction with a settlement agreement that the Company and VectorY B.V. entered into in April 2021. In the year ended December 31, 2022, the Company recognized \$0.3 million of other income related to the equity stake received in VectorY. No such income was recorded in the year ending December 31, 2020.

In 2022, 2021 and 2020 the Company's other income also consisted of income from the subleasing of a portion of the Amsterdam facility while other expense consists of expenses incurred in relation to the subleasing income.

17. Income taxes

a. Income tax (benefit) / expense

Due to the uncertainty surrounding the realization of favorable tax attributes in future tax returns, the Company has recorded a valuation allowance against the Company's net deferred tax assets in the Netherlands. The Company released a full valuation allowance against the Company's net deferred tax assets in the United States as of December 31, 2020.

In connection with the Corlieve acquisition, the Company recognized a deferred tax liability related to acquired identifiable intangible assets and a deferred tax asset for net operating tax loss carryforwards for a net of EUR 11.9 million (\$14.2 million) as of the Acquisition Date.

There are no significant unrecognized tax benefits as of December 31, 2022 and 2021.

For the years ended December 31, 2022, 2021 and 2020, (loss) / income before income tax benefit / (expense) consists of the following:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
Dutch operations	\$ (96,872)	\$ 348,400	\$ (130,493)
U.S. operations	(14,934)	(12,737)	(10,950)
Other	(16,453)	(2,857)	—
Total	\$ (128,259)	\$ 332,806	\$ (141,443)

The income tax benefit / (expense) for the years ended December 31, 2022, 2021 and 2020, consists of the following:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
Current tax (expense)			
Other	\$ (24)	\$ (7)	\$ —
Total current tax (expense)	\$ (24)	\$ (7)	\$ —
Deferred tax benefit / (expense)			
Dutch operations	\$ (808)	\$ (3,047)	\$ —
U.S. operations	(1,075)	(771)	16,419
Other	3,377	608	—
Total deferred tax benefit / (expense)	\$ 1,494	\$ (3,210)	\$ 16,419
Total income tax benefit / (expense)	\$ 1,470	\$ (3,217)	\$ 16,419

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 (loss) / income before income tax benefit / (expense) for the years ended December 31, 2022, 2021 and 2020, is as follows:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
(Loss) / income before income tax benefit / (expense) for the period	\$ (128,259)	\$ 332,806	\$ (141,443)
Expected income tax benefit / (expense) at the tax rate enacted in the Netherlands (2022: 25.8%, 2021: 25.0%, 2020: 25.0%)	33,091	(83,201)	35,361
Non-deductible expenses	(11,129)	(9,182)	(5,041)
Other net change in valuation allowance	(20,591)	88,857	(30,568)
Difference in tax rates between the Netherlands and the U.S. as well as other foreign countries	99	309	247
Release of valuation allowance related to expected future taxable income of U.S. operations	—	—	16,419
Income tax benefit / (expense)	\$ 1,470	\$ (3,217)	\$ 16,419

Non-deductible expenses predominantly relate to share-based compensation expenses. These expenses affected the effective tax rate by an amount of \$8.5 million in 2022 (2021: \$6.7 million; 2020: \$5.8 million). The fair value loss on contingent consideration affected the effective tax rate by an amount of \$1.9 million in 2022 (\$2.0 million and nil in 2021 and 2020, respectively).

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 as of December 31, 2022 and 2021 are as follows:

	Years ended December 31,	
	2022	2021
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	\$ 84,633	\$ 71,917
Operating lease liabilities	10,612	9,300
Intangible assets	3,826	2,039
Accrued expenses and other current liabilities	1,862	1,312
Property, plant and equipment	510	971
Inventory	—	148
Research and development tax credit carryforwards	144	105
Interest carryforwards	3,697	—
Total deferred tax assets	\$ 105,284	\$ 85,792
Less valuation allowance	(74,547)	(60,289)
Deferred tax assets, net of valuation allowance	\$ 30,737	\$ 25,503
Acquired IPR&D Intangible Asset	(15,033)	(15,189)
Operating lease right-of-use assets	(9,323)	(7,493)
Other current assets and receivables	(110)	(87)
Deferred tax liability	\$ (24,466)	\$ (22,769)
Net deferred tax asset	\$ 6,271	\$ 2,734

Changes in the valuation allowance were as follows:

	Years ended December 31,		
	2022	2021	2020
	(in thousands)		
January 1,	\$ 60,289	\$ 150,113	\$ 109,856
Changes recorded in the statement of operations	20,593	(88,858)	30,568
Changes recorded in equity	(972)	—	—
Increase related to 2021 and 2020 Dutch tax reforms	—	1,897	18,287
Valuation allowance assumed in Corlieve acquisition	—	545	—
Release of valuation allowance related to expected current year and future periods recorded in profit and loss	—	—	(16,419)
Other changes including currency translation adjustments	(5,363)	(3,408)	7,821
December 31,	\$ 74,547	\$ 60,289	\$ 150,113

The Company released the full valuation allowance against the Company's net deferred assets in the United States as of December 31, 2020. Included within changes recorded in the statement of operations for the year ended December 31, 2020 are benefits of \$1.2 million from the utilization of U.S. net operating loss carryforwards.

The valuation allowance as of December 31, 2022 is primarily related to net operating loss carryforwards in the Netherlands.

Netherlands

As of December 31, 2022, the total amount of net operating losses carried forward under the Dutch tax regime was \$264.0 million (December 31, 2021: \$228.5 million, 2020: \$588.2 million). The Company has historically recorded a full valuation allowance. The Company evaluates all positive and negative evidence including future income from the CSL Behring Agreement in assessing the need for such a full valuation allowance. Management considered reversing taxable temporary differences, projected future taxable income and tax-planning strategies in making this assessment. The Company concluded that as of December 31, 2022, December 31, 2021 and December 31, 2020 it is more likely than not that the remaining deferred tax assets will not be realized.

The Company recorded \$462.4 million of license revenue in May 2021 after the Closing of the CSL Behring transaction. The Company recorded such revenue in its Dutch tax return related to the 12-month period ended December 31, 2020, which it filed on February 10, 2022. As such, the Company filed a return showing a taxable profit in the Netherlands in 2020, which resulted in the consumption of substantially all of its Dutch net operating losses for the years 2011 to 2018. The Company's remaining Dutch net operating tax losses carried forward relate to 2019 and 2022. The Company allocated the tax benefit from the release of the valuation allowance related to net operating loss carryforwards generated by share issuance cost incurred in 2014, 2015, 2017 and 2018 to additional paid-in capital. This resulted in an increase of additional paid-in capital as well as deferred tax expenses of \$3.0 million during the year ended December 31, 2021.

The Company recorded \$0.8 million increase of additional paid-in capital in the year ended December 31, 2022 resulting from the release of valuation allowance for the tax benefit of share issuance costs incurred in 2018, 2019 and 2021.

A portion of the valuation allowance for deferred tax assets recorded as of December 31, 2022 continues to relate to follow-on offering costs incurred in 2019. Any subsequently recognized tax benefits will be credited directly to contributed capital. As of December 31, 2022, that amount was \$3.3 million (\$4.5 million as of December 31, 2021).

The Dutch corporate tax rate for fiscal years 2020 and 2021 was 25.0%. In December 2021, further changes were enacted that raised the corporate income tax rate from 25.0% to 25.8% from 2022 onwards.

In June 2021 legislation was enacted allowing for an indefinite carryforward from fiscal year 2022 onwards of existing and future net operating loss carryforwards subject to a limit of offsetting taxable profit in excess of EUR 1.0 million to 50% of the taxable profit.

The fiscal periods from 2020 onwards are still open for inspection by the Dutch tax authorities.

United States of America

The federal corporate tax rate in the U.S. is 21.0%. In addition, the Company is subject to state income taxes resulting in a combined tax rate of 27.32% for its U.S. operation. As of December 31, 2022, an estimated \$38.5 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 to 2022. The Company expects to continue to generate taxable income in the U.S. during the foreseeable future.

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 from 2019 are still open for inspection by the Internal Revenue Service ("IRS"). To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the IRS or Massachusetts Department of Revenue to the extent utilized in a future period. The Company is currently not under examination by the IRS for any tax years.

France

The French corporate tax rate for fiscal year 2022 was 25%. In addition, the Company is subject to a surcharge of 3.3% of the 25.0% standard corporate tax rate resulting in a combined rate of 25.8%.

The Company's French operation has incurred losses since incorporation and is expected to continue incurring tax losses for the foreseeable future.

The French operation as of December 31, 2022 has an estimated \$23.3 million of taxable losses that are available for carry forward indefinitely.

18. Basic and diluted earnings per share

Basic net (loss) / income per ordinary share is computed by dividing net (loss) / income for the period by the weighted average number of ordinary shares outstanding during the period. Diluted earnings per ordinary share are calculated by adjusting the weighted average number of ordinary shares outstanding, assuming conversion of all potentially dilutive ordinary shares. For the year ended December 31, 2021, dilutive net income / (loss) per ordinary share is computed using the treasury method. As the Company has incurred a loss in the years ended December 31, 2022 and December 31, 2020, all potentially dilutive ordinary shares for these years would have an antidilutive effect, if converted, and thus have been excluded from the computation of loss per share for the years ended December 31, 2022 and December 31, 2020.

	Year ended December 31,		
	2022	2021	2020
	(in thousands, except share amounts)		
Numerator:			
Net (loss) / income attributable to ordinary shares	\$ (126,789)	\$ 329,589	\$ (125,024)
	<u>(126,789)</u>	<u>329,589</u>	
Denominator:			
Weighted-average number of ordinary shares outstanding - basic	46,735,045	45,986,467	44,466,365
Stock options under 2014 Plans and previous plan	—	746,044	—
Non-vested RSUs and PSUs	—	107,162	—
Employee share purchase plan	—	1,299	—
Weighted-average number of ordinary shares outstanding - diluted	<u>46,735,045</u>	<u>46,840,972</u>	<u>44,466,365</u>

The following table presents ordinary share equivalents that were excluded from the calculation of diluted net income / (loss) per ordinary share for the years ended December 31, 2022, 2021 and 2020 as the effect of their inclusion would have been anti-dilutive:

	Year ended December 31,		
	2022	2021	2020
Anti-dilutive ordinary share equivalents			
Stock options under 2014 Plans and previous plan	4,237,917	2,576,281	2,673,279
Non-vested RSUs and PSUs	2,219,464	1,236,385	679,958
Employee share purchase plan	1,048	1,842	560
Total anti-dilutive ordinary share equivalents	<u>6,458,429</u>	<u>3,814,508</u>	<u>3,353,797</u>

The anti-dilutive ordinary shares are presented without giving effect to the application of the treasury method or exercise prices that exceeded the price of the Company's ordinary shares as of December 31, 2022 and December 31, 2020.

19. 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. The Company also has obligations to make future payments that become due and payable upon the collection of milestone payments from CSL Behring. The achievement and timing of these milestones is not fixed and determinable. Relevant commitments and contingencies are further discussed in other sections of this form 10-K, such as, Note 3 "*Corlieve transaction*" and Note 4 "*Collaboration arrangements and concentration of credit risk*", amongst others.

20. 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, 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 4 "*Collaboration arrangements and concentration of credit risk*") as well as the elimination of the BMS warrants (see Note 7, "*Fair value measurement*").

21. Subsequent events

On January 31, 2023, the Company announced that it had entered into a global licensing agreement for a gene therapy for amyotrophic lateral sclerosis caused by mutations in superoxide dismutase 1 with Apic Bio. The Company made an initial cash payment of \$10.0 million. In addition, the Company will pay Apic Bio up to \$43.0 million in milestones upon achievement of regulatory approvals in the U.S. and Europe and pre-specified annual net sales, and a tiered royalty on net sales ranging from the mid-single digits to low double digits.

EXHIBIT INDEX

Exhibit No.	Description
2.1†	Sale and Purchase Agreement, executed June 21, 2021, by and between uniQure N.V. and Corlieve Therapeutics SAS (incorporated by reference to Exhibit 2.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2021 filed with the Securities and Exchange Commission).
3.1	Amended Articles of Association of the Company (incorporated by reference to Exhibit 3.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2021 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 Plan (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).
10.6t	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).
10.18	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).
10.27†	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).
10.36t	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).
10.40	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.
10.49t	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).
10.53†	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 (incorporated by reference to Exhibit 10.57 of the Company's annual report on Form 10-K for the year ended December 31, 2020 (file no. 0001-36294) filed with the Securities and Exchange commission).
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. (incorporated by reference to Exhibit 10.58 of the Company's annual report on Form 10-K for the year ended December 31, 2020 (file no. 0001-36294) filed with the Securities and Exchange commission).
10.59	Cooperation Agreement, dated as of April 16, 2021, by and among uniQure N.V., ForUniqure B.V., Forbion 1 Management B.V., Forbion International Management B.V., and Forbion Capital Partners Management Holding B.V. (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, 2021 filed with the Securities and Exchange Commission).
10.60t	2014 Share Incentive Plan, Amended and Restated, effective as of June 16, 2021 (incorporated by reference to Exhibit 4.1 of the Company's quarterly report on Form 10-Q (file no. 001-36294) for the period ending on June 30, 2021 filed with the Securities and Exchange Commission).
10.61t	Employment Agreement, effective May 17, 2021, by and between uniQure biopharma B.V. and Pierre Caloz (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, 2021 filed with the Securities and Exchange Commission).
10.62t	Equity Side Letter, effective May 17, 2021, by and between uniQure N.V. and Pierre Caloz (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, 2021 filed with the Securities and Exchange Commission).
10.63t	Amended and Restated Employment Agreement, effective June 15, 2021, by and between uniQure biopharma B.V. and Christian Klemt (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 June 30, 2021 filed with the Securities and Exchange Commission).

10.64	Consent and Amendment No. 3 to Second Amended and Restated Loan and Security Agreement, dated July 30, 2021, by and among the Registrant, Hercules Capital Inc., and the other parties named therein (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, 2021 filed with the Securities and Exchange Commission).
10.65†	Form of Share Option Agreement, effective December 8, 2021, under the 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.65 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
10.66†	Form of Restricted Stock Unit Award, effective December 8, 2021, under the 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.66 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
10.67††	Form of Performance Stock Unit Award, effective December 8, 2021 under the 2014 Share Incentive Plan (incorporated by reference to Exhibit 10.67 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
10.68†	Third Amended and Restated Loan and Security Agreement as of December 15, 2021, by and among uniQure biopharma B.V., uniQure Inc., uniQure IP B.V., the Company and Hercules Capital Inc (incorporated by reference to Exhibit 10.68 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
10.69†	Lease Agreement relating to 20 Maguire Road, Lexington, Massachusetts, dated as of December 22, 2021, by and between uniQure Inc. and G&I IX/GP4 20 Maguire LLC (incorporated by reference to Exhibit 10.69 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
10.70†	Lease Agreement relating to 91 Hartwell Avenue, Lexington, Massachusetts, dated as of February 1, 2022, by and between uniQure Inc. and NRL 91 Hartwell LLC (incorporated by reference to Exhibit 10.70 of the Company's annual report on Form 10-K for the year ended December 31, 2021 (file no. 001-36294) filed with the Securities and Exchange Commission).
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.
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*	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

[Table of Contents](#)

101*	The following materials from the Company's Annual Report on Form 10-K for the year ended December 31, 2022, 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, 2022, 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.

UNIQUE, N.V.

Date: February 27, 2023

By: /s/ MATTHEW KAPUSTA
Matthew Kapusta
Chief Executive Officer (Principal Executive Officer)

Date: February 27, 2023

By: /s/ CHRISTIAN KLEMT
Christian Klemt
Chief Financial Officer (Principal 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.

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<u>/s/ MATTHEW KAPUSTA</u> Matthew Kapusta	Chief Executive Officer and Director (Principal Executive Officer)	February 27, 2023
<u>/s/ CHRISTIAN KLEMT</u> Christian Klemt	Chief Financial Officer (Principal Financial Officer)	February 27, 2023
<u>/s/ MADHAVAN BALACHANDRAN</u> Madhavan Balachandran	Director	February 27, 2023
<u>/s/ ROBERT GUT</u> Robert Gut	Director	February 27, 2023
<u>/s/ RACHELLE JACQUES</u> Rachelle Jacques	Director	February 27, 2023
<u>/s/ JACK KAYE</u> Jack Kaye	Director	February 27, 2023
<u>/s/ DAVID MEEK</u> David Meek	Director	February 27, 2023
<u>/s/ LEONARD POST</u> Leonard Post	Director	February 27, 2023
<u>/s/ PAULA SOTEROPOULOS</u> Paula Soteropoulos	Director	February 27, 2023
<u>/s/ JEREMY P. SPRINGHORN</u> Jeremy P. Springhorn	Director	February 27, 2023

**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 80,000,000 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 subsequently are typically reappointed for a term of a maximum of two years, which reappointment may be extended by 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 14, 2022, 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 14, 2022, 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.

SUBSIDIARIES OF UNIQUE N.V.

Name of Subsidiary	Jurisdiction of Organization
uniQure biopharma B.V.	The Netherlands
uniQure IP B.V.	The Netherlands
uniQure Inc.	Delaware
Corlieve Therapeutics SAS	France
Corlieve Therapeutics AG	Switzerland

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-253749) on Form S-3 and (No. 333-258036, No. 333-225629, No. 333-222051, No. 333-218005 and No. 333-197887) on Form S-8 of our report dated February 27, 2023, with respect to the consolidated financial statements of uniQure N.V. and the effectiveness of internal control over financial reporting.

/s/ KPMG Accountants N.V.

Amstelveen, The Netherlands

February 27, 2023

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
(Principal Executive Officer)
February 27, 2023

Certification of Chief Financial Officer

I, Christian Klemt, 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/ CHRISTIAN KLEMT

Christian Klemt
Chief Financial Officer
(Principal Financial Officer)
February 27, 2023

**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, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Matthew Kapusta, Chief Executive Officer, and Christian Klemt, Chief Financial Officer of the Company, hereby certify, 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
(Principal Executive Officer)
February 27, 2023

By: /s/ CHRISTIAN KLEMT

Christian Klemt
Chief Financial Officer
(Principal Financial Officer)
February 27, 2023

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.
