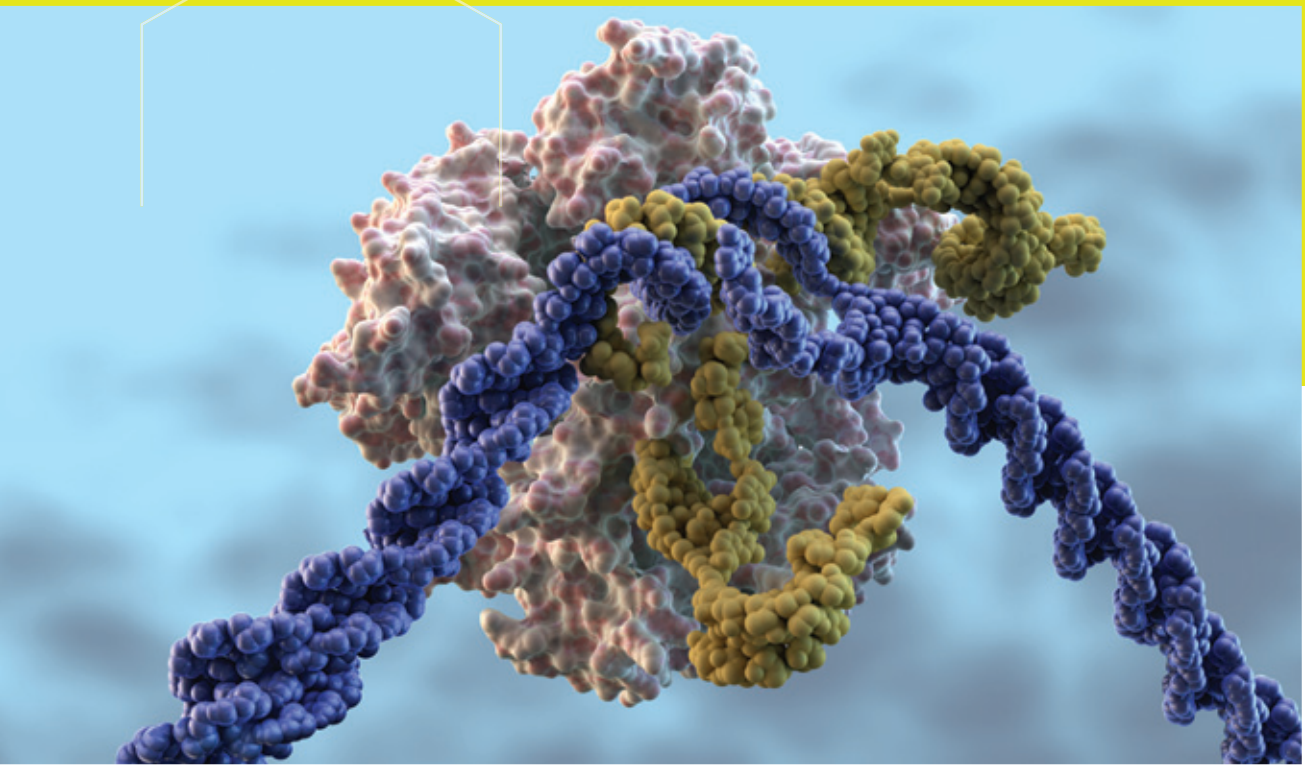
Transformative Gene-Based Medicines

For Serious Human Diseases

2022 ANNUAL REPORT

CRISPR THERAPEUTICS®



We are rapidly translating our specific, efficient and versatile CRISPR/Cas9 gene-editing platform into therapies to treat serious human diseases

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 001-37923

CRISPR THERAPEUTICS AG

(Exact name of registrant as specified in its charter)

Switzerland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Baarerstrasse 14 **6300 Zug, Switzerland**	
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +41 (0)41 561 32 77

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Shares, nominal value CHF 0.03	**CRSP**	**The Nasdaq Global Market**

Securities registered pursuant to 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 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, 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 Exchange Act). YES ☐ NO ☒

The aggregate market value of the common shares held by non-affiliates of the Registrant was approximately $4.3 billion, based on the closing price on the Nasdaq Global Market of the Registrant's common shares on June 30, 2022 (the last trading day of the Registrant's second fiscal quarter of 2022).

The number of the Registrant's common shares outstanding as of February 16, 2023 was 78,646,679.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the 2023 Annual General Meeting of Shareholders, which the Registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A within 120 days after the end of the Registrant's fiscal year ended December 31, 2022, are incorporated by reference into Part III of this Report.

Table of Contents

Risk Factor Summary

Our business is subject to a number of risks and uncertainties of which you should be aware before making an investment decision in our business. These risks are discussed more fully in the "Risk Factors" section of this Annual Report on Form 10-K. These risks include, but are not limited to, the following:

- We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.
- We will need to raise substantial additional funding, which will dilute our shareholders. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate some of our product development programs or commercialization efforts.
- If we are unable to advance our product candidates to clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.
- Our CRISPR/Cas9 gene editing product candidates are based on a relatively new gene editing technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all. There have only been a limited number of clinical trials of product candidates based on gene editing technology and no gene editing products have been approved in the United States or in the European Union.
- The U.S. Food and Drug Administration, or FDA, the National Institutes of Health, or NIH, and the European Medicines Agency, or 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, which may be difficult to predict.
- If any of the product candidates we may develop or the delivery modes we rely on cause undesirable side effects, it could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.
- If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.
- Our business may be adversely affected by a pandemic, epidemic or outbreak of an infectious disease, such as the ongoing coronavirus pandemic and the emergence of additional variants.
- Positive results from early preclinical studies or preliminary results from clinical trials of our product candidates are not necessarily predictive of the results of later preclinical studies and any future clinical trials of our product candidates. If we cannot replicate the positive results from our earlier preclinical studies of our product candidates in our later preclinical studies, clinical trials and future clinical trials, we may be unable to successfully develop, obtain regulatory approval for and commercialize our product candidates.
- Adverse public perception of gene editing and cellular therapy products may negatively impact demand for, or regulatory approval of, our product candidates.
- The commercial success of any of our product candidates will depend upon its degree of market acceptance by physicians, patients, third-party payors and others in the medical community.
- We face significant competition in an environment of rapid technological change. Our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may harm our business and financial condition, and our ability to successfully market or commercialize our product candidates.
- Our collaborators and strategic partners may control aspects of our clinical trials, which could result in delays and other obstacles in the commercialization of our proposed products and materially harm our results of operations.
- Gene editing products are novel and may be complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business.
- If we are unable to obtain or protect intellectual property rights related to our proprietary gene editing technology and product candidates, we may not be able to compete effectively in our markets.
- The intellectual property landscape around gene editing technology, including CRISPR/Cas9, is highly dynamic, and third parties may initiate legal proceedings alleging that the patents that we in-license or own are invalid or that we are infringing, misappropriating, or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Throughout this Annual Report on Form 10-K, the "Company," "CRISPR," "CRISPR Therapeutics," "we," "us," and "our," except where the context requires otherwise, refer to CRISPR Therapeutics AG and its consolidated subsidiaries, and "our board of directors" refers to the board of directors of CRISPR Therapeutics AG.

"CRISPR Therapeutics®" standard character mark and design logo, "COBALT™," "CRISPRX™," "CRISPR TX™," "CTX001™," "CTX110®," "CTX112™," "CTX120™," "CTX121™," "CTX130™," "CTX131™," "CTX310™," "CTX320™," "CTX330™," "VCTX210™" and "VCTX211™," are trademarks and registered trademarks of CRISPR Therapeutics AG. All other trademarks and registered trademarks contained in this Annual Report on Form 10-K are the property of their respective owners. Solely for convenience, trademarks, service marks and trade names referred to in this Annual Report on Form 10-K may appear without the ® or ™ symbols and any such omission is not intended to indicate waiver of any such rights.

Special Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K contains "forward-looking statements" that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K are forward-looking statements. These statements are often identified by the use of words such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "predict," "project," "potential," "will," "would" or the negative or plural of these words or similar expressions or variations, although not all forward-looking statements contain these identifying words. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the safety, efficacy and clinical progress of our various clinical programs, including those for exa-cel (formerly known as CTX001), CTX110, CTX112, CTX130, CTX131, VCTX210 and VCTX211;
- the status of clinical trials, development timelines and discussions with regulatory authorities related to product candidates under development by us and our collaborators;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, including our ongoing clinical trials and any planned clinical trials, and our research and development programs, including delays or disruptions in clinical trials, non-clinical experiments and Investigational New Drug application-enabling studies;
- the actual or potential benefits of FDA designations, such as orphan drug, fast track and regenerative medicine advanced therapy, or such European equivalents, including the PRIority MEdicines, or PRIME, designation, as well as anticipated regulatory filings for exa-cel and the timing of such regulatory submissions to the FDA;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the size and growth potential of the markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates and the success of competing therapies that are or become available;
- our plan to validate our cell therapy manufacturing facility to enable us to produce clinical cell therapy product supply in the future;
- our intellectual property coverage and positions, including those of our licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property;
- our anticipated expenses, ability to obtain funding for our operations and the sufficiency of our cash resources;
- the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies; and
- potential impacts due to the coronavirus pandemic on our business, financial condition and results of operations.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and assumptions that could cause our actual results and the timing of certain events to differ materially from future results expressed or implied by the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified herein, and those discussed in the section titled "Risk Factors," set forth in Part I, Item 1A of this Annual Report on Form 10-K. You should not rely upon forward-looking statements as predictions of future events. Such forward-looking statements speak only as of the date of this report. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make or enter into.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results, performance or achievements may be materially different from what we expect. Except as required by law, we undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date of such statements.

This Annual Report on Form 10-K includes statistical and other industry and market data, which we obtained from our own internal estimates and research, as well as from industry and general publications and research, surveys, and studies conducted by third

parties. Industry publications, studies, and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

PART I

Item 1. Business.

BUSINESS

Overview

We are a leading gene editing company focused on the development of CRISPR/Cas9-based therapeutics. CRISPR/Cas9 stands for Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) and is a revolutionary technology for gene editing, the process of precisely altering specific sequences of genomic DNA. We aim to apply this technology to disrupt, delete, correct and insert genes to treat genetically defined diseases and to engineer advanced cellular therapies. We believe that our scientific expertise, together with our gene editing approach, may enable an entirely new class of highly effective and potentially curative therapies for patients with both rare and common diseases for whom current biopharmaceutical approaches have had limited success.

The use of CRISPR/Cas9 for gene editing was derived from a naturally occurring viral defense mechanism in bacteria and was co-invented by one of our scientific founders, Dr. Emmanuelle Charpentier, the Acting and Founding Director of the Max Planck Unit for the Science of Pathogens in Berlin, Germany. Dr. Charpentier and her collaborators published work elucidating the mechanism by which the Cas9 endonuclease, a key component of CRISPR/Cas9, can be programmed to cut double-stranded DNA at specific locations. Dr. Charpentier and her collaborator, Dr. Jennifer Doudna of the University of California, Berkeley, shared the 2020 Nobel Prize in Chemistry for their groundbreaking work. We have acquired rights to the intellectual property encompassing CRISPR/Cas9 and related technologies from Dr. Charpentier and continue to strengthen our intellectual property estate through our own research and additional in-licensing efforts, furthering our leadership in the development of CRISPR/Cas9-based therapeutics.

We have established a portfolio of therapeutic programs in a broad range of disease areas across four core franchises: hemoglobinopathies, immuno-oncology, regenerative medicine and *in vivo* approaches. Our most advanced programs target the genetically defined diseases transfusion-dependent beta thalassemia, or TDT, and severe sickle cell disease, or SCD, two hemoglobinopathies with high unmet medical need. We are also progressing several gene-edited allogeneic cell therapy programs, including allogeneic chimeric antigen receptor T cell, or CAR T, candidates for the treatment of hematological and solid tumor cancers, and investigational, allogeneic, gene-edited, immune-evasive, stem cell-derived therapies for the treatment of type 1 diabetes, or T1D. In addition, we are advancing multiple programs leveraging *in vivo* editing approaches, initially for the treatment and prevention of cardiovascular disease.

Our product development and partnership strategies are designed to exploit the full potential of the CRISPR/Cas9 platform while maximizing the probability of successfully developing our product candidates. For our most advanced product candidates, we have taken an *ex vivo* approach in which we edit cells outside of the human body using CRISPR/Cas9 before administering them to the patient. In contrast, for our *in vivo* editing programs, we deliver the CRISPR/Cas9-based therapeutic directly to target cells within the human body.

Hemoglobinopathies

Our lead product candidate, exagamglogene autotemcel, or exa-cel, formerly known as CTX001, is an investigational, autologous, *ex vivo* CRISPR gene-edited hematopoietic stem cell therapy that is being evaluated for patients suffering from TDT or severe SCD, in which a patient's hematopoietic stem cells are engineered *ex vivo* to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells. HbF is a form of the oxygen-carrying hemoglobin that is naturally present at birth and is then replaced by the adult form of hemoglobin. The elevation of HbF by exa-cel has the potential to eliminate transfusion requirements for TDT patients and painful and debilitating vaso-occlusive crises for SCD patients. Exa-cel is being developed under a joint development and commercialization agreement between us and Vertex Pharmaceuticals Incorporated, or Vertex.

We and Vertex are investigating exa-cel in two ongoing Phase 1/2/3 open-label clinical trials that are designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 12 to 35 with TDT (CLIMB-111) or SCD (CLIMB-121), respectively. Enrollment is complete for both CLIMB-111 and CLIMB-121. We and Vertex have also initiated two additional Phase 3 open-label clinical trials of exa-cel in pediatric patients with TDT (CLIMB-141) and SCD (CLIMB-151). Patients who received exa-cel in CLIMB-111, CLIMB-121, CLIMB-141 or CLIMB-151 will be asked to participate in a long-term, open-label follow-up trial, CLIMB-131, to evaluate the safety and efficacy of exa-cel. CLIMB-131 is designed to follow participants for up to 15 years after exa-cel infusion. In the second and fourth quarters of 2022, at the European Hematology Association Congress and American Society of Hematology Annual Meeting, respectively, we presented updated clinical data from CLIMB-111 and CLIMB-121 for 44 patients with TDT and 31 patients with SCD treated with exa-cel. For additional information regarding the clinical data, please see "*Our Lead Hemoglobinopathies Product Candidate—exa-cel*."

Exa-cel has been granted a number of regulatory designations from the U.S. Food and Drug Administration, or FDA, specifically Regenerative Medicine Advanced Therapy, or RMAT, Fast Track, Orphan Drug, and Rare Pediatric Disease designations for the treatment of both TDT and SCD. Exa-cel has also been granted Orphan Drug Designation from the European Commission, as well as the PRIority MEdicines, or PRIME, designation from the European Medicines Agency, or EMA, for the treatment of both TDT and SCD. For additional information regarding the impact of regulatory designations, please see "*Business—Government Regulations* ."

In December 2022, we and Vertex completed regulatory submissions for exa-cel with the EMA and the Medicines and Healthcare products Regulatory Agency, or MHRA, in the EU and the UK, respectively, and both the EMA and the MHRA have validated the Marketing Authorization Application, or MAA, respectively. In addition, we and Vertex initiated the rolling submission of our Biologics Licensing Application, or BLA, in the United States in November 2022 and expect to complete the submission by the end of the first quarter of 2023.

Finally, building upon exa-cel, we have next-generation efforts in targeted conditioning regimens and *in vivo* editing of hematopoietic stem cells, either of which could broaden the number of patients that could benefit from our therapies.

Immuno-Oncology

We believe CRISPR/Cas9 has the potential to create the next generation of CAR T cell therapies that may have a superior product profile compared to current autologous therapies and allow accessibility to broader patient populations. Drawing from the *ex vivo* gene editing capabilities gained through our lead programs, we are advancing several immuno-oncology cell therapy programs, including allogeneic CAR T programs targeting CD19 and CD70.

CD19 Franchise

CTX110, our lead immuno-oncology product candidate, is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting Cluster of Differentiation 19, or CD19. We are investigating CTX110 in our CARBON clinical trials, which are designed to assess the safety and efficacy of CTX110 in adult patients with relapsed or refractory CD19-positive B-cell malignancies who have received at least two prior lines of therapy. CTX110 has been granted RMAT designation by the FDA.

The Phase 1 CARBON clinical trial is being conducted in two parts – Part A and Part B. In Part A of the Phase 1 CARBON clinical trial, or Phase 1 Part A, patients were infused with a single dose of CTX110 across escalating dose levels following a standard lymphodepletion regimen, with an option to re-dose CTX110 based on clinical benefit. In Part B of the Phase 1 CARBON clinical trial, or Phase 1 Part B, patients received CTX110 at Dose Level (DL) 4 following standard lymphodepletion, as well as a consolidation dose of CTX110 at the same dose level between four and eight weeks after the initial dose for patients that demonstrated clinical benefit.

In the fourth quarter of 2022, we presented updated clinical data from Phase 1 Part A for 32 patients treated with CTX110, which showed the potential for CTX110 to achieve long-term durable complete remissions, or CRs, with a positively differentiated safety profile in heavily pre-treated patients, and described emerging data from Phase 1 Part B, which showed an encouraging efficacy profile with the potential to improve efficacy with the use of a consolidation dose. For additional information regarding the clinical data, please see "*Our Lead Immuno-Oncology Product Candidate—CTX110*." Based on this emerging data from our Phase 1 CARBON clinical trial and discussions with regulatory agencies, we have expanded CARBON to include a Phase 2, potentially registrational, single-arm, multi-center, open-label clinical trial that incorporates consolidation dosing. We have begun dosing patients in this pivotal arm.

In parallel with CTX110, we are advancing CTX112, a next-generation investigational, allogeneic CAR T product candidate targeting CD19. CTX112 includes two additional edits beyond CTX110, making use of the fact that our CRISPR/Cas9 platform enables us to innovate continuously by incorporating incremental edits into next-generation products. These edits target the genes encoding Regnase-1 and transforming growth factor-beta receptor type 2 (TGFBR2) with the aim of enhancing CAR T potency and reducing CAR T exhaustion. In the fourth quarter of 2022, the Investigational New Drug, or IND, application for CTX112 was cleared by the FDA.

CD70 Franchise

CTX130 is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting Cluster of Differentiation 70, or CD70, an antigen expressed on various solid tumors and hematologic malignancies. CTX130 is being investigated in two ongoing independent Phase 1, single-arm, multi-center, open-label clinical trials that are designed to assess the safety and efficacy of several dose levels of CTX130 in adult patients. The COBALT-LYM trial is evaluating the safety and efficacy of CTX130 for the treatment of relapsed or refractory T or B cell malignancies. The COBALT-RCC trial is evaluating the safety and efficacy of CTX130 for the treatment of relapsed or refractory clear cell renal cell carcinoma. CTX130 has received Orphan Drug Designation from the FDA for the treatment of T cell lymphoma and RMAT designation for the treatment of Mycosis Fungoides and Sézary Syndrome (MF/SS), subtypes of Cutaneous T cell Lymphoma (CTCL). In the second quarter of 2022, at the European Hematology Association Congress, we released initial clinical data from the ongoing COBALT-LYM trial for 18 patients with T cell lymphoma treated with

CTX130 who had reached at least 28 days of follow-up. Also, in the fourth quarter of 2022, at the Society of Immuno-therapy in Cancer Annual Meeting, we released initial clinical data from the COBALT-RCC trial for 14 patients. For additional information regarding the clinical data, please see "*CTX130.*"

In parallel with CTX130, we are advancing CTX131, a next-generation investigational, allogeneic CAR T product candidate targeting CD70 for the potential treatment of both solid tumors and certain hematologic malignancies. CTX131 includes two additional edits beyond CTX130. These edits, the same used in CTX112, target the genes encoding Regnase-1 and TGFBR2 with the aim of enhancing CAR T potency and reducing CAR T exhaustion; and in the first quarter of 2023, the IND for CTX131 was cleared by the FDA.

Additional candidates

We are advancing several additional CAR T product candidates. For two such candidates, we have developed an innovative partnership model with leading cancer centers to validate the novel targets Cluster of Differentiation 83, or CD83, and glypican-3, or GPC3, in the clinic. In partnership with Moffitt Cancer Center, we are advancing an autologous CAR T candidate targeting CD83, which has potential to treat acute myeloid leukemia and other oncology and autoimmune indications. With Roswell Park Comprehensive Cancer Center, we are advancing a gene-edited, autologous CAR T candidate targeting GPC3, expressed in hepatocellular carcinoma. In both cases, our academic partners will conduct manufacturing and first-in-human clinical trials. This structure will enable us to assess the safety and activity of these targets rapidly. Based on the clinical results, we can choose to continue advancing these autologous programs internally or develop allogeneic versions to expand the opportunity further. In addition, beyond CAR T, we formed a collaboration with Nkarta, Inc., or Nkarta, that brings together our gene editing technology and cell therapy expertise with Nkarta's leading natural killer (NK) cell discovery, development and manufacturing capabilities. As part of that collaboration we and Nkarta are co-developing and co-commercializing a donor-derived, gene-edited CAR-NK cell product candidate targeting CD70.

Regenerative Medicine

Regenerative medicine, or the use of stem cells to repair or replace tissue or organ function lost due to disease, damage or age, holds great potential to treat both rare and common diseases. Building upon our *ex vivo* gene editing expertise, we have expanded our efforts in this field with a focus on allogeneic stem cell-derived therapies gene edited using CRISPR/Cas9 to enable immune evasion, improve cell function, and direct cell fate. Our first major effort in this area is in diabetes, and we and ViaCyte, Inc., which was acquired by Vertex in the third quarter of 2022, or ViaCyte, are advancing a series of programs as part of a strategic collaboration for the discovery, development and commercialization of gene-edited stem cell therapies for the treatment of diabetes. We believe the combination of ViaCyte's stem cell capabilities and our gene editing capabilities has the potential to enable a beta-cell replacement product candidate that may deliver durable benefit to patients without requiring concurrent immune suppression.

We have a multi-staged product strategy that leverages our CRISPR/Cas9 platform to advance multiple product candidates incorporating incremental edits designed to increase benefit. Our initial product candidate, VCTX210, is an investigational, allogeneic, gene-edited, immune-evasive, stem cell-derived product candidate for the treatment of T1D developed by applying our gene editing technology to ViaCyte's proprietary stem cell capabilities. VCTX210 has gene edits designed to promote immune evasion and cell fitness. We and ViaCyte are investigating VCTX210 in an ongoing Phase 1 clinical trial that is designed to assess VCTX210's safety, tolerability, and immune evasion in patients with T1D, and are in the follow-up stage for this clinical trial. Our next generation product candidate, VCTX211, is an investigational, allogeneic, gene-edited, stem cell-derived product candidate for the treatment of T1D, which incorporates additional gene edits that aim to further enhance cell fitness. In the fourth quarter of 2022, the Clinical Trial Application for VCTX211 was cleared by Health Canada and the Phase 1/2 clinical trial is ongoing.

In Vivo

In addition to our *ex vivo* programs, we are pursuing a number of *in vivo* gene editing programs. Our *in vivo* gene editing strategy focuses on gene disruption and whole gene correction – the two technologies required to address the vast majority of the most prevalent severe monogenic diseases. We have established a leading platform for *in vivo* gene disruption, starting in the liver. We plan to advance a broad portfolio of programs across both rare and common diseases with this platform, starting with cardiovascular diseases, or CVD. Our lead investigational *in vivo* programs, CTX310 and CTX320, target angiopoietin-related protein 3 (ANGPTL3) and lipoprotein(a) (Lp(a)), respectively, two validated targets for CVD. Gene editing has the potential to shift the treatment paradigm for CVD by recapitulating the proven benefit of natural human genetic variants in a single-dose format. In addition, we continue to develop an expansive whole gene correction platform, starting with using lipid nanoparticles, or LNP, and adeno-associated viral vectors, or AAV, in the liver and advancing to AAV-free, homology-directed repair (HDR)-independent methodologies.

CRISPR-X

While we have made significant progress with our current portfolio of programs, we recognize that we need to continue to innovate to unlock the full potential of CRISPR gene editing and bring the potential of transformative therapies to even more patients.

In 2022, we launched a new early-stage research team known as CRISPR-X that focuses on innovative research to develop next-generation editing modalities. CRISPR-X focuses on technologies to enable whole gene correction and insertion without requiring HDR or viral delivery of DNA, such as all-RNA gene correction, non-viral delivery of DNA and novel gene insertion techniques.

Partnerships

Given the numerous potential therapeutic applications for CRISPR/Cas9, we have partnered strategically to broaden the indications we can pursue and accelerate development of programs by accessing specific technologies and/or disease-area expertise. We maintain broad partnerships to develop gene editing-based therapeutics in specific disease areas. For additional information regarding certain of these partnerships, please see "*Business—Strategic Partnerships and Collaborations*."

Vertex. We established our initial collaboration agreement in 2015 with Vertex, which focused on TDT, SCD, cystic fibrosis and select additional indications. In December 2017, we entered into a joint development and commercialization agreement with Vertex pursuant to which, among other things, we are co-developing and preparing to co-commercialize exa-cel for TDT and SCD. In April 2021, we and Vertex amended and restated our existing joint development and commercialization agreement, pursuant to which, among other things, we will continue to develop and prepare to commercialize exa-cel for TDT and SCD in partnership with Vertex. We also entered into a strategic collaboration and license agreement with Vertex in June 2019 for the development and commercialization of products for the treatment of Duchenne muscular dystrophy, or DMD, and myotonic dystrophy type 1, or DM1.

ViaCyte. We entered into a research and collaboration agreement in September 2018 with ViaCyte to pursue the discovery, development and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes, and in July 2021, we entered into a joint development and commercialization agreement with ViaCyte, or the ViaCyte JDCA. In connection with entering into the ViaCyte JDCA, our existing research collaboration agreement with ViaCyte expired in accordance with its terms. Under the ViaCyte JDCA, we and ViaCyte are jointly developing and will commercialize product candidates and shared products for use in the treatment of diabetes type 1, diabetes type 2 and insulin dependent/requiring diabetes, or the ViaCyte Collaboration Field, throughout the world. The ViaCyte JDCA includes, among other things, provisions relating to collaboration and program governance, clinical activities for the product candidates and shared products under the agreement and continuing research by the parties in the ViaCyte Collaboration Field. Unless otherwise mutually agreed, research costs incurred by a party will be solely borne by such party. The program expenses, as originally set forth in the research and collaboration agreement, as applicable, incurred through the date of first commercial sale of a shared product will be allocated 60% to us and 40% to ViaCyte. Following first commercial sale of a shared product, such program expenses will be shared equally between us and ViaCyte. Shared product revenues will be shared equally by us and ViaCyte. In the third quarter of 2022, Vertex announced it had acquired ViaCyte and the rights to the ViaCyte Collaboration Field.

Bayer. We entered into an option agreement in the fourth quarter of 2019 with Bayer Healthcare LLC, or Bayer, pursuant to which Bayer has an option to co-develop and co-commercialize two products that we advance for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders for a specified period of time, or, under certain circumstances, exclusively license such optioned products.

Other Partnerships. We have entered into a number of additional collaborations and license agreements to support and complement our hematopoietic stem cell, immuno-oncology, regenerative medicine and *in vivo* programs and platform, including agreements with: Nkarta to co-develop and co-commercialize two donor-derived, gene-edited CAR-NK cell product candidates and a product candidate combining NK and T cells; Capsida Biotherapeutics, Inc. to develop *in vivo* gene editing therapies delivered with engineered AAV vectors for the treatment of amyotrophic lateral sclerosis and Friedreich's ataxia; Moffitt Cancer Center and Roswell Park Comprehensive Cancer Center to advance autologous CAR T programs against new targets; MaxCyte, Inc. on *ex vivo* delivery for our hemoglobinopathy and immuno-oncology programs; CureVac AG on optimized mRNA constructs and manufacturing for certain *in vivo* programs; and KSQ Therapeutics, Inc. on intellectual property for our allogeneic immuno-oncology programs.

Our mission is to create transformative gene-based medicines for serious human diseases. We believe that our highly experienced team, together with our scientific expertise, product development strategy, partnerships and intellectual property, position us as a leader in the development of CRISPR-based therapeutics.

Gene Editing Background

There are thousands of diseases caused by aberrant DNA sequences. Traditional small molecule and biologic therapies have had limited success in treating many of these diseases because they fail to address the underlying genetic causes. Newer approaches such as RNA therapeutics and viral gene therapy more directly target the genes related to disease, but each has clear limitations. RNA-based therapies, such as mRNA and siRNA, face challenges with repeat dosing and related toxicities. Non-integrating viral gene therapy platforms, such as AAV, may have limited durability because they do not permanently change the genome and have limited efficacy upon re-administration due to resulting immune responses. Integrating viral gene therapy platforms, such as lentivirus, permanently alter the genome but do so randomly, which leads to the potential for undesirable mutations. Additionally, cells may recognize the transduced genes as foreign and respond by reducing their expression, limiting their efficacy. Thus, while our

understanding of genetic diseases has increased since the mapping of the human genome, our ability to treat them effectively has been limited.

We believe gene editing has the potential to enable a next generation of therapeutics and provide potentially curative therapies to many genetic diseases through precise gene modification. Furthermore, the ability to alter DNA sequences precisely has applications beyond the treatment of genetically defined diseases. CRISPR/Cas9 gene editing could also enable the engineering of cell-based therapies to make them more efficacious, safer and available to a broader group of patients. Cell therapies have already begun to make a meaningful impact in certain diseases and gene editing could help accelerate that progress across diverse disease areas, including oncology and diabetes.

The process of gene editing involves precisely altering DNA sequences within the genomes of cells using enzymes to cut the DNA at specific locations. After a cut is made, natural cellular processes repair the DNA to either silence or correct undesirable sequences, potentially reversing their negative effects. Importantly, because the genome itself is modified in this process, the change is permanent in the patient. Earlier generations of gene editing technologies, such as zinc finger nucleases, or ZFNs, transcription-activator like effector nucleases, or TALENs, and meganucleases, rely on engineered protein-DNA interactions to govern the location of editing. While these systems were an important first step to demonstrate the potential of gene editing, their development has been challenging in practice due to the complexity of engineering protein-DNA interactions. In contrast, CRISPR/Cas9 is guided by RNA-DNA interactions, which are more predictable and straightforward to engineer and apply. As a result, we have continued to invest in broadening our CRISPR platform so we can employ a variety of technologies as appropriate.

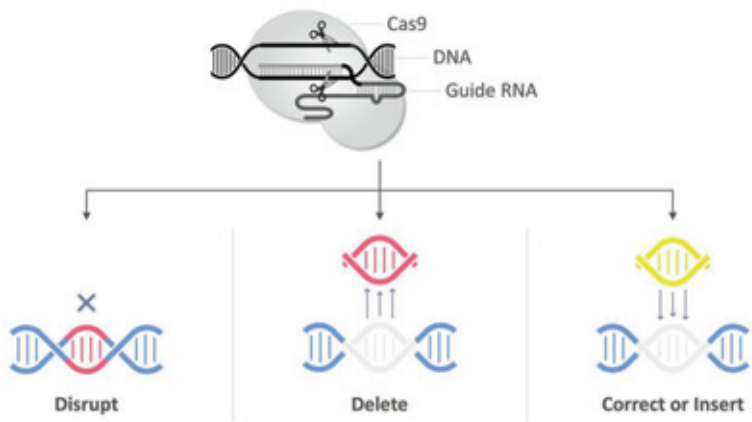
The CRISPR/Cas9 Technology

CRISPR/Cas9 evolved as a naturally occurring defense mechanism that protects bacteria against viral infections. Dr. Charpentier and her collaborators elucidated this mechanism and developed ways to adapt and simplify it for use in gene editing. In recognition of this groundbreaking work, Dr. Charpentier was awarded the 2020 Nobel Prize in Chemistry along with her collaborator, Dr. Jennifer Doudna of the University of California, Berkeley. The CRISPR/Cas9 technology they described consists of three basic components: CRISPR-associated protein 9, or Cas9, CRISPR RNA, or crRNA, and trans-activating CRISPR RNA, or tracrRNA. Cas9, in combination with these two RNA molecules, is described as “molecular scissors” that can make specific cuts and edits in selected double-stranded DNA.

Dr. Charpentier and her collaborators further simplified the system for use in gene editing by combining the crRNA and tracrRNA into a single RNA molecule called a guide RNA. The guide RNA binds to Cas9 and can be programmed to direct the Cas9 enzyme to a specific DNA sequence based on Watson-Crick base pairing rules. The CRISPR/Cas9 technology can be used to make cuts in DNA at specific sites of targeted genes, providing a powerful tool for developing gene editing-based therapeutics.

Once the DNA is cut, the cell uses naturally occurring DNA repair mechanisms to rejoin the cut ends. If a single cut is made, a process called non-homologous end joining can result in the addition or deletion of base pairs, disrupting the original DNA sequence and causing gene inactivation. A larger fragment of DNA can also be deleted by using two guide RNAs that target separate sites. After cleavage at each site, non-homologous end joining unites the separate ends, deleting the intervening sequence. Alternatively, if a DNA template is added alongside the CRISPR/Cas9 machinery, the cell can correct a gene or even insert a new gene through a process called homology-directed repair.

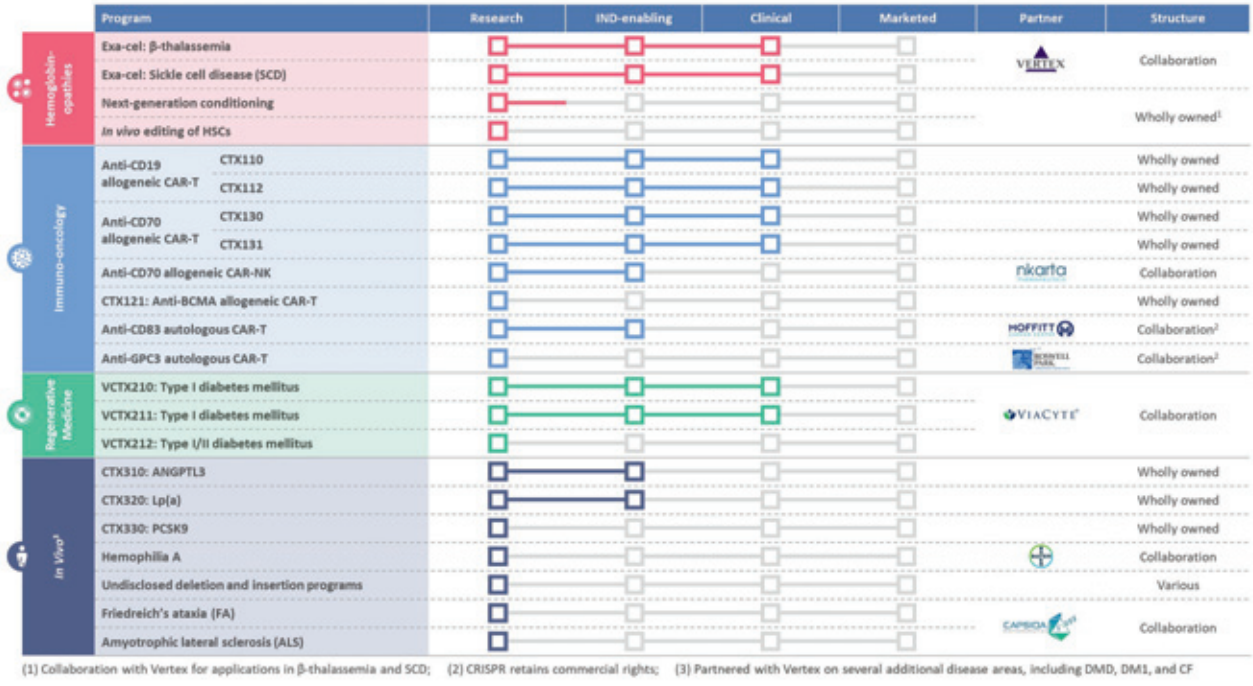
CRISPR/Cas9 gene editing



We believe that CRISPR/Cas9 is a versatile technology that can be used to disrupt, delete, correct or insert genes. We intend to take advantage of the versatility and modularity of the CRISPR/Cas9 system to adapt and rapidly customize individual components for specific disease applications. Consequently, we believe that CRISPR/Cas9 may form the basis of a new class of therapeutics with the potential to treat both rare and common diseases. Given the advantages of CRISPR/Cas systems, multiple academic groups have developed new technologies based on CRISPR/Cas9, such as base editing and prime editing. While still nascent, such new CRISPR/Cas-based technologies could have advantages over existing gene editing technologies, including CRISPR/Cas9 technologies, in select applications. As a result, we have continued to invest in broadening our CRISPR platform so we can employ a variety of technologies as appropriate.

Our Pipeline

The following table summarizes the status of our product development pipeline:



Hemoglobinopathies

We are primarily utilizing *ex vivo* approaches to treat diseases related to the hematopoietic system, which is the system of organs and tissues, such as bone marrow, the spleen and lymph nodes, involved in the production of blood. Today, many of the hematopoietic system diseases we are targeting are treated with allogeneic hematopoietic stem cell transplants, or allo-HSCT. In performing allo-HSCT, physicians replace a patient's blood-forming cells that contain the defective gene with cells obtained from a different person that contain the normal gene. Unfortunately, not all patients are able to be matched with suitable donors. Patients who do undergo allo-HSCT face a high risk of complications such as infections related to immunosuppression, transplant rejection and graft-versus-host disease, where immune cells in the transplanted tissue (the graft) recognize the recipient (the host) as "foreign" and begin to attack the host's cells.

In contrast to allo-HSCT, our approach is to harvest stem cells directly from the patient, edit the target gene *ex vivo*, and reintroduce those same cells back into the patient. We believe this *ex vivo* gene editing approach, which uses the patient's own cells, may provide better results than allo-HSCT.

Our Lead Programs—Hemoglobinopathies

Hemoglobinopathies are a diverse group of inherited blood disorders that result from variations in the synthesis or structure of hemoglobin. Our lead program in hemoglobinopathies, for which we have partnered with Vertex, aims to develop a single, potentially curative CRISPR/Cas9-based therapy to treat both TDT and SCD. These diseases are caused by mutations in the gene encoding the

beta globin protein. Beta globin is an essential component of hemoglobin, a protein in red blood cells that delivers oxygen and removes carbon dioxide throughout the body. Several factors make these attractive lead indications, including: (i) high unmet medical need, (ii) compelling market potential, (iii) well-understood genetics and (iv) the ability to employ an *ex vivo* gene disruption strategy.

Beta Thalassemia

Overview

Beta thalassemia is a blood disorder that is associated with a reduction in the production of hemoglobin. This disease is caused by mutations that give rise to the insufficient expression of the beta globin protein, which can lead to symptoms related not only to the lack of hemoglobin, but also to the buildup of unpaired alpha globin proteins in red blood cells. The severity of symptoms associated with beta thalassemia varies depending on the levels of functional beta globin present in the blood cells. The unpaired alpha globin chains are toxic to red blood cells and reduce red blood cell lifespan. In the most severe cases, described as beta thalassemia major, functional beta globin is either completely absent or reduced, resulting in severe anemia. In these patients, the bone marrow cannot keep pace with the destruction of red blood cells, and thus these patients require regular blood transfusions. While chronic blood transfusions can be effective at addressing symptoms, they often lead to iron overload, progressive heart and liver failure, and eventually early death. Patients with mild forms of beta thalassemia may experience some mild anemia or even be asymptomatic. The total worldwide incidence of beta thalassemia is estimated to be 60,000 births annually, the total prevalence in the United States and the European Union, or EU, is estimated to be approximately 16,000 and there are over 200,000 people worldwide who are alive and registered as receiving treatment for the disease.

Limitations of current treatment options

The most common treatment for beta thalassemia is chronic blood transfusions. Transfusion-dependent patients typically receive transfusions every two to four weeks and chronic administration of blood often leads to elevated levels of iron in the body, which can cause organ damage over a relatively short period of time. Patients are often given iron chelators, or medicines to reduce iron levels in the blood, which are associated with their own significant toxicities. In developing countries, where chronic transfusions are not available, most patients die in early childhood. Also, a disease-modifying therapy for beta thalassemia, Reblozyl (luspatercept-aamt), received FDA approval in 2019.

A potentially curative therapy for beta thalassemia is allo-HSCT, but few patients elect to have this procedure given its associated morbidity and mortality and the lack of matched and willing donors. In addition, the EMA gave a conditional marketing authorization to Zynteglo (autologous $CD34^+$ cells encoding $\beta^{A\text{-}T87Q}$-globin gene), a lentiviral gene therapy developed by bluebird bio, for the treatment of certain patients with TDT in 2019, but in 2021 bluebird bio withdrew Zynteglo from the European market, after failing to reach agreement with health authorities on the treatment's price. The FDA approved Zynteglo in August 2022. We believe that our therapeutic approach could offer a potentially curative therapy for this devastating disease.

Sickle Cell Disease

Overview

SCD is an inherited disorder of red blood cells resulting from a specific mutation in the beta globin gene that causes abnormal red blood cell function. Under conditions of low oxygen concentration, the abnormal hemoglobin proteins aggregate within the red blood cells causing them to become sickled in shape and inflexible. These sickled cells obstruct blood vessels, restricting blood flow to organs, ultimately resulting in severe pain, infections, stroke, overall poor quality of life and early death. Patients also experience increased hemolysis, leading to anemia. The worldwide incidence of SCD is estimated to be 300,000 births annually and there are 20-25 million people worldwide with the disease. In the United States and the European Union, the total prevalence is estimated to be 150,000 individuals.

Limitations of current treatment options

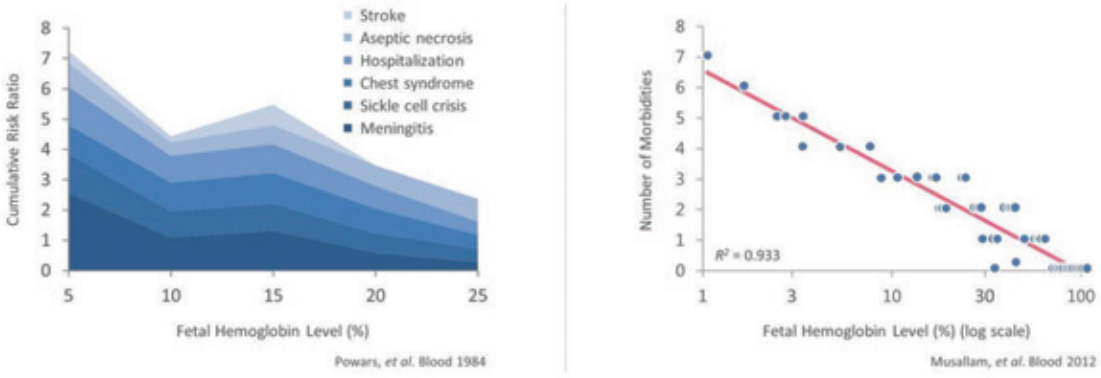
As with beta thalassemia, in regions where medical infrastructure can support it, standard treatment for patients with SCD who have high levels of hemolysis involves chronic blood transfusions, which has the same associated risks of iron overload and toxicities associated with chelation therapy. The FDA and/or EMA have approved several disease-modifying therapies for SCD as well, including hydroxyurea, Adakveo (crizanlizumab-tmca) and Oxbryta (voxelotor). Allo-HSCT is another potential treatment option. While allo-HSCT provides the only potentially curative therapeutic path for SCD, it is often avoided given the significant risk of transplant-related morbidity and mortality in these patients and the lack of matched and willing donors.

Our Gene Editing Approach

Our therapeutic approach to treating beta thalassemia and SCD employs gene editing to upregulate the expression of the gamma globin protein, a hemoglobin subunit that is commonly present only in newborn infants. Hemoglobin that contains gamma globin instead of beta globin protein is referred to as fetal hemoglobin, or HbF. In most individuals HbF disappears in infancy as gamma

globin is replaced by beta globin through naturally occurring suppression of the gamma globin gene. The symptoms of beta thalassemia and SCD typically do not manifest until several months after birth, when the levels of HbF have declined considerably. Some patients with beta thalassemia or SCD have elevated levels of HbF that persist into adulthood, a condition known as hereditary persistence of fetal hemoglobin, or HPFH. Patients with HPFH are often asymptomatic, or experience much milder forms of disease. This protective HPFH condition has been shown to result from specific changes to these patients' genomic DNA, either in the region of the globin genes or in certain genetic regulatory elements that control the expression levels of the globin genes.

Relationship between level of HbF and morbidity in sickle cell disease and beta thalassemia



An alternative CRISPR/Cas9 approach to treating hemoglobinopathies would be to correct the mutated beta globin gene. We have chosen the HbF upregulation strategy as our initial approach given the efficiency and consistency of the gene disruption strategy involved, the ability of this strategy to counteract a wide variety of different beta globin mutations, including patients with beta thalassemia, and the natural history data supporting absence of symptoms in patients with HPFH.

Our Lead Hemoglobinopathies Product Candidate—exa-cel

Our lead product candidate, exa-cel, uses CRISPR/Cas9 to mimic the high levels of HbF that occur naturally in HPFH patients. To achieve this effect, exa-cel uses CRISPR/Cas9 to disrupt the erythroid specific enhancer of the *BCL11A* gene. This gene encodes the BCL11A protein, a critical factor that keeps HbF levels low in most individuals. Disrupting the BCL11A erythroid specific enhancer reduces BCL11A expression specifically in erythroid lineage cells, thereby upregulating expression of gamma globin and increasing HbF levels.

Our therapeutic approach involves isolating hematopoietic stem cells, or HSCs, which give rise to red blood cells, from a patient, treating those cells *ex vivo* with CRISPR/Cas9 to disrupt the BCL11A erythroid specific enhancer and reintroducing the edited cells back into the patient. We believe that once reintroduced into the patient, these genetically modified stem cells will produce red blood cells that contain high levels of HbF. In beta thalassemia, elevating HbF may reduce the toxicity of unpaired alpha globin chains, thereby increasing red blood cell lifespan. Consequently, exa-cel has the potential to reduce or even eliminate the need for transfusions in these patients. In SCD, elevated HbF may prevent a cell from sickling, and so achieving sufficiently high HbF in most red blood cells could significantly reduce or eliminate the symptoms associated with the disease.

We believe our CRISPR/Cas9 gene editing strategy may have significant advantages over other gene therapies in development for the treatment of hemoglobinopathies. For example, lentivirus-based treatments involve a random integration of one or more copies of the globin gene throughout the genome. The expression levels of the newly introduced gene can vary depending on the exact location of the DNA in the genome, leading to inconsistent and variable levels of expression. We believe our strategy may lead to more uniform globin expression across a high percentage of cells. In addition, with each random lentiviral integration, a mutation may be created, which may have an associated safety concern, including the oncogenetic potential. In contrast, CRISPR/Cas9 targets a specific genomic site for editing, and to date we have detected no off-target activity for our exa-cel guide RNA.

Preclinical Studies

In preclinical studies, our CRISPR/Cas9 gene editing process demonstrated the ability to edit HSCs with approximately 80% allelic editing efficiency at clinical scale in a bulk population of cells. We observed this high editing efficiency across all stem cell subsets, including in long-term repopulating HSCs. After *in vitro* erythroid differentiation, this editing resulted in HbF accounting for greater than 30% of total hemoglobin in edited cells, compared to approximately 10% HbF in the control arm of the study. On a per cell basis, more than 90% of cells had modifications at the desired location, with 76% of the cells having edits in both copies of the

target gene and 16% of the cells having edits made on one copy of the target gene. We estimate that after *in vitro* erythroid differentiation this editing rate results in HbF expression levels of greater than 35% in cells that have edits on both copies of the target gene, and over 20% for cells edited at one gene.

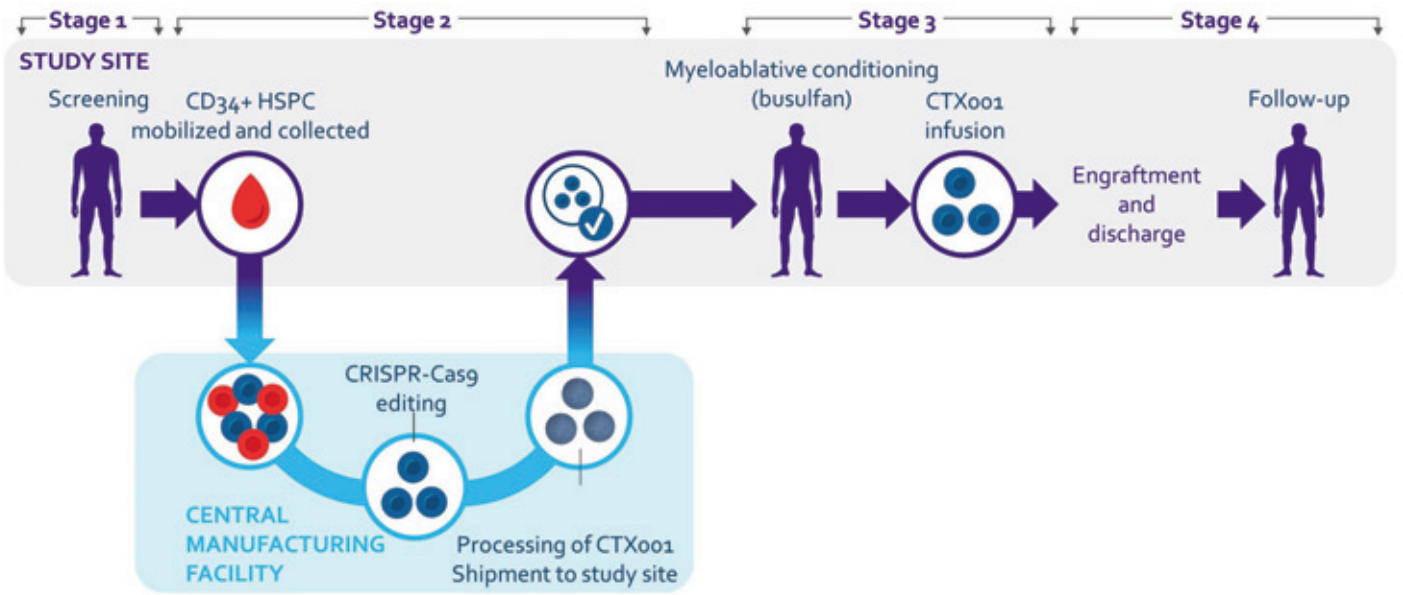
In preclinical mouse models designed to test the safety of exa-cel, gene-edited HSCs maintained the ability to engraft long term and to differentiate into multiple lineages. Toxicology studies revealed no significant findings and no difference in the biodistribution of edited cells compared to controls. Finally, no off-target activity was detectable for the exa-cel guide RNA after assessing over 5,000 homology-based sites and over 2,000 homology-independent sites.

Clinical Trials

We and Vertex are investigating exa-cel in two ongoing Phase 1/2/3 open-label clinical trials that are designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 12 to 35 with TDT, CLIMB-111, and severe SCD, CLIMB-121, respectively. The first two patients in each clinical trial were treated sequentially and, following data from the initial two patients in each clinical trial indicating successful engraftment and an acceptable safety profile, that clinical trial opened for concurrent dosing. Both clinical trials are designed to follow patients for approximately two years after infusion. Enrollment is complete for both CLIMB-111 and CLIMB-121. We and Vertex have also initiated two additional Phase 3 open-label clinical trials of exa-cel in pediatric patients with TDT, CLIMB-141, and SCD, CLIMB-151. Patients who received exa-cel in CLIMB-111, CLIMB-121, CLIMB-141 or CLIMB-151 will be asked to participate in a long-term, open-label follow-up trial, CLIMB-131, to evaluate the safety and efficacy of exa-cel. CLIMB-131 is designed to follow participants for up to 15 years after exa-cel infusion.

Exa-cel has been granted a number of regulatory designations from the U.S. Food and Drug Administration, or FDA, specifically RMAT, Fast Track, Orphan Drug, and Rare Pediatric Disease designations for the treatment of both TDT and SCD. Exa-cel has also been granted Orphan Drug Designation from the European Commission, as well as PRIME designation from the European Medicines Agency, for the treatment of both TDT and SCD. In December 2022, we and Vertex completed regulatory submissions for exa-cel with the EMA and MHRA in the EU and the UK, respectively, and both the EMA and the MHRA have validated the MAA, respectively. In addition, we and Vertex initiated the rolling submission of our BLA in the United States in November 2022 and expect to complete the submission by the end of the first quarter of 2023.

Schematic of study procedures for the CLIMB-111 and CLIMB-121 Phase 1/2/3 clinical trials

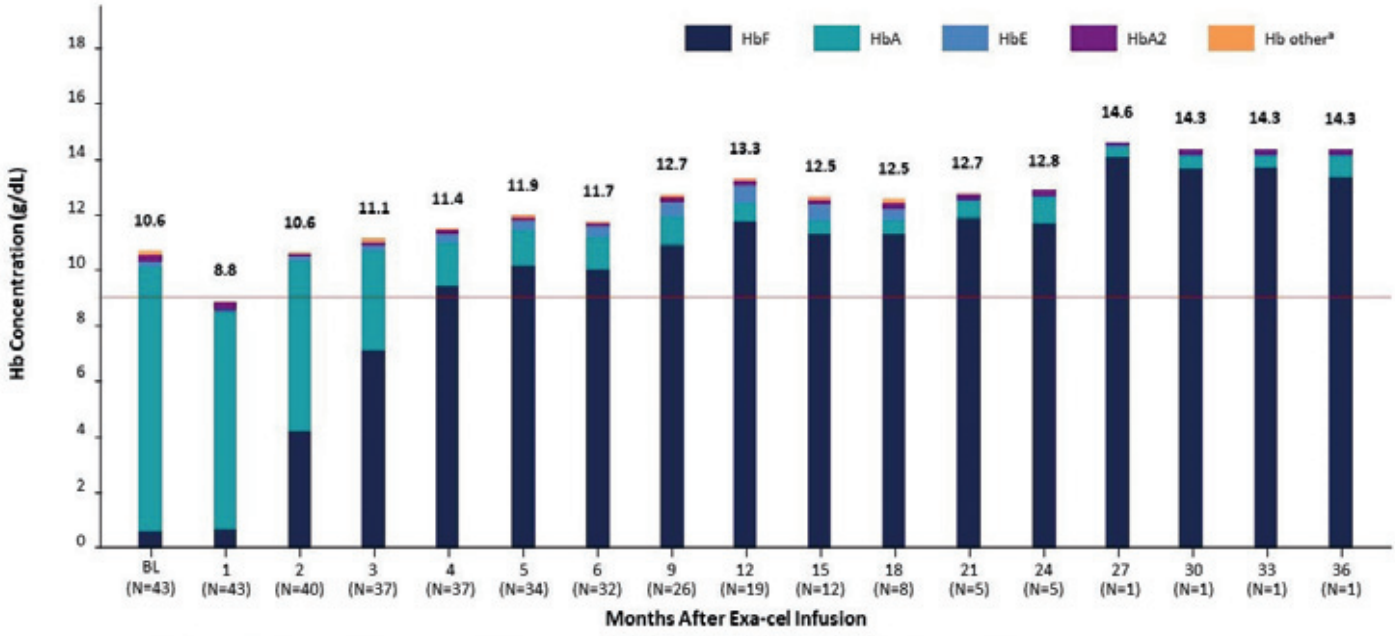


CLIMB-111 Trial in TDT

In the second and fourth quarters of 2022, at the European Hematology Association (EHA) Congress and American Society of Hematology (ASH) Annual Meeting, respectively, we presented clinical data from 44 patients with TDT treated with exa-cel as of the February 2022 data cutoff. With a median follow-up of 11.9 months (range: 1.2 to 37.2 months), 42 of 44 patients with TDT treated with exa-cel were transfusion-free (0.8-36.2 months) and the two patients who had not yet stopped transfusions had reduced transfusion volume by 75% and 89%, respectively. All 44 patients showed a similar pattern of response, with rapid and sustained increases in total hemoglobin and HbF, pancellular distribution of HbF, and reduction or elimination of packed red blood cell transfusions soon after exa-cel infusion. All 12 patients with the severe beta zero/beta zero genotype evaluable for elimination of transfusions were transfusion-free since last follow-up. In addition, the available bone marrow allelic editing data demonstrated

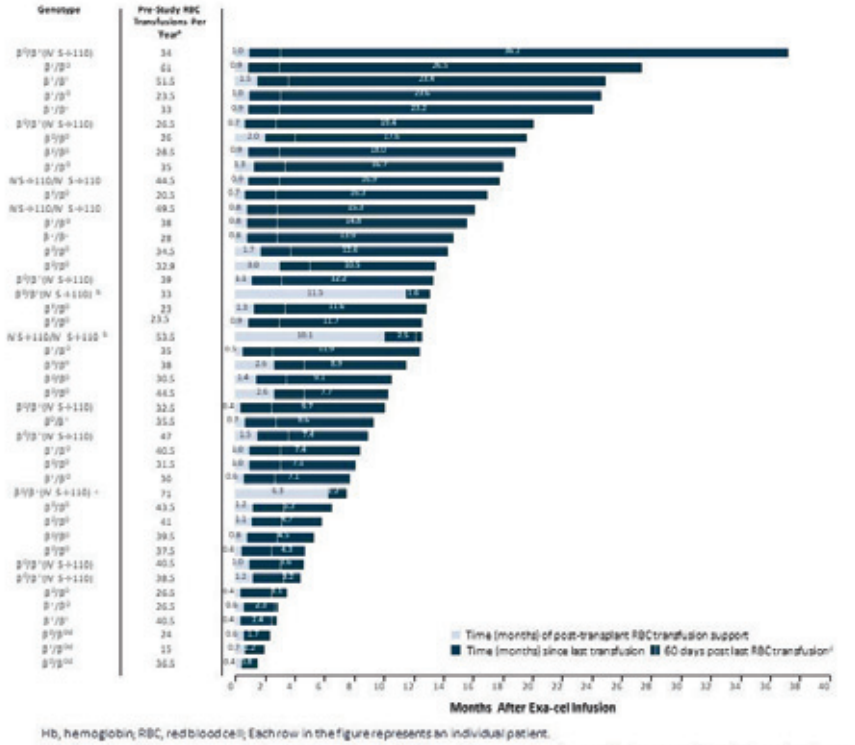
durability over time. Consistent with this bone marrow allelic editing data, all 19 patients with greater than one year of follow-up as of the data cutoff date demonstrate a stable and durable response to treatment, including the first patient treated with exa-cel, who had a total hemoglobin level of 14.3 g/dL at last visit, three years after exa-cel dosing.

Clinically Meaningful HbF and Total Hb Were Achieved Early and Maintained in TDT



BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin, alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; TDT, transfusion-dependent β-thalassemia.
Mean total Hb concentrations are shown directly above bars.
[a]Hb adducts and other variants.

Duration of Transfusion Independence After Exa-cel Infusion



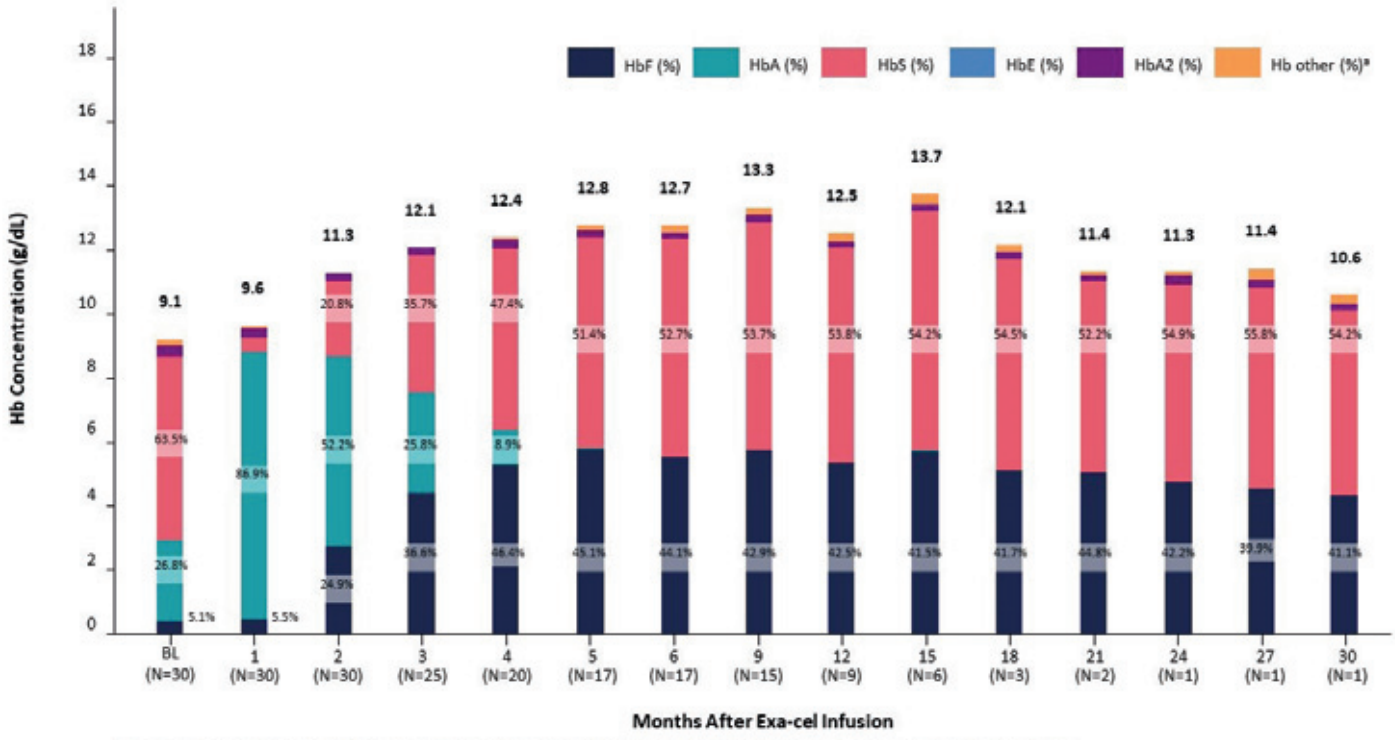
Hb, hemoglobin; RBC, red blood cell; Each row in the figure represents an individual patient.
[a]Number of transfusion units annualized over 2 years; [b]Received RBC transfusions at or after data cut; [c]Patient stopped transfusions after data cut; [d]Patients are evaluable for elimination of transfusions starting 60 days after their last transfusion.

The safety data from all 44 patients were generally consistent with an autologous stem cell transplant and myeloablative conditioning. Two patients experienced serious adverse events, or SAEs, assessed by the investigator as related or possibly related to exa-cel. One patient had three SAEs related to exa-cel of hemophagocytic lymphohistiocytosis (HLH; macrophage activation syndrome), acute respiratory distress syndrome, and headache, and one SAE of idiopathic pneumonia syndrome related to both exa-cel and busulfan. All events began peri-engraftment, occurred in the context of HLH and fully resolved with steroid and immunosuppressant treatment. Another patient had SAEs related to both exa-cel and busulfan of delayed neutrophil engraftment and thrombocytopenia. Both SAEs resolved and neutrophil engraftment was achieved on Day 56 without use of backup cells. All other patients achieved neutrophil engraftment within 43 days of exa-cel infusion. No SAEs related to exa-cel were reported in the other patients.

CLIMB-121 Trial in Severe SCD

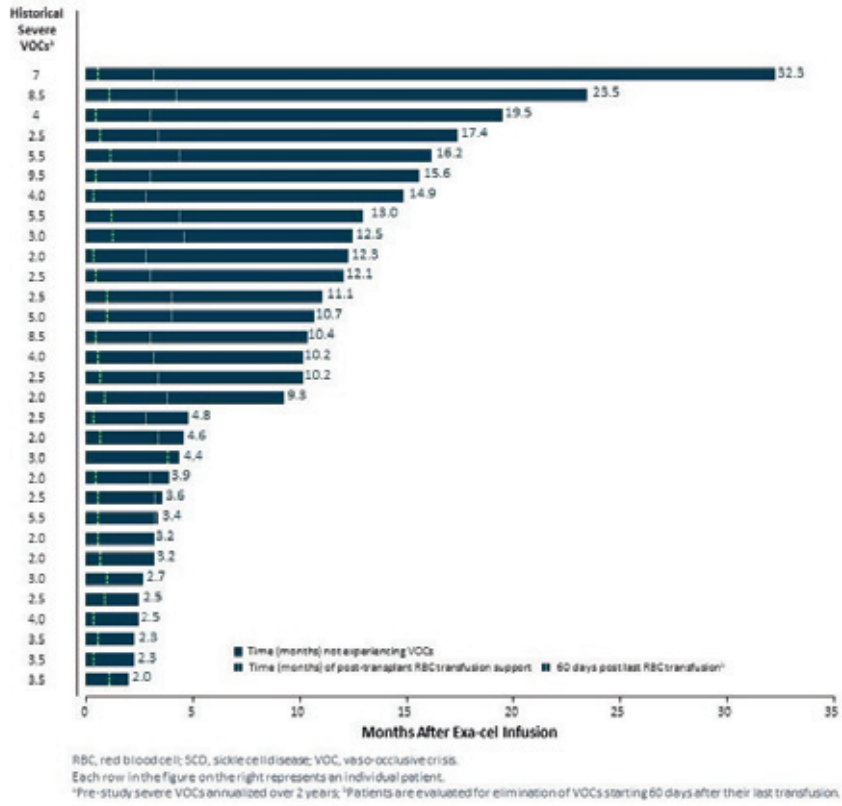
In the second and fourth quarters of 2022, at the EHA Congress and ASH Annual Meeting, respectively, we presented clinical data from 31 patients with SCD treated with exa-cel as of the February 2022 data cutoff. With a median follow-up of 10.2 months (range: 2.0 to 32.3 months), all 31 patients had elimination of vaso-occlusive crises, or VOCs, after exa-cel infusion and remain VOC-free at last visit. All patients showed a similar pattern of response, with rapid and sustained increases in total hemoglobin and HbF, and pancellular distribution of HbF. Mean total hemoglobin levels exceeded 12 g/dL by Month 4, with mean proportion of HbF above 40%. In addition, the available bone marrow allelic editing data demonstrated durability over time. All nine patients with greater than one year of follow-up as of the data cutoff date demonstrate a stable and durable response to treatment, including the first patient with SCD treated with exa-cel, who had a total hemoglobin level of 10.6 g/dL and HbF fraction of 41% at last visit, 30 months after exa-cel dosing.

Clinically Meaningful HbF and Total Hb Were Achieved Early and Maintained in SCD



BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin, alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; HbS, sickle hemoglobin; SCD, sickle cell disease.
Bars show mean Hb (g/dL). Labels indicate mean proportion of HbS and HbF as a percentage of total Hb. Mean total Hb concentrations are shown directly above bars.
[a]Hb adducts and other variants.

Duration of Freedom from VOCs after Exa-cel Infusion



RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Each row in the figure on the right represents an individual patient.
[1]Pre-study severe VOCs annualized over 2 years; [2]Patients are evaluated for elimination of VOCs starting 60 days after their last transfusion.

The safety data from all 31 patients were generally consistent with an autologous stem cell transplant and myeloablative conditioning. There were no SAEs considered related or possibly related to exa-cel, and the majority of non-serious adverse events were considered mild to moderate. After the data cut in February 2022, an adult patient with SCD developed pneumonia and respiratory failure following SARS-CoV-2 infection, resulting in death. The investigator assessed the events as due to SARS-CoV-2 infection, with a potential contribution of busulfan lung injury, and unrelated to exa-cel.

Next-generation Efforts

Building upon exa-cel, we have next-generation efforts in targeted conditioning regimens, which could offer benefits over the myeloablative busulfan conditioning regimen currently used with exa-cel, as well as for *in vivo* editing of hematopoietic stem cells, either of which could broaden the number of patients that can benefit from our therapies.

Immuno-Oncology

Interest in the oncology community has grown rapidly in the field of immuno-oncology, or treatments that harness the immune system to attack cancer cells. Engineered immune cell therapy is one such approach, in which immune system cells such as T cells are genetically modified to enable them to recognize and attack cancerous cells.

Engineered cell therapy has demonstrated encouraging results leading to multiple approvals for autologous CAR T products. These therapies may become an entirely new class of oncology therapeutics, but realizing this full potential will require overcoming some key challenges. Most engineered cell therapies in development require unique products to be created for each patient treated, an approach that has in the past proven challenging and cost prohibitive in the field of oncology. This bespoke manufacturing process takes time during which a patient's disease can progress and sometimes fails to produce a viable product at all. Additionally, these versions of engineered cell therapies appear limited in their ability to treat solid tumors and have demonstrated a high rate of toxicities that require complicated management protocols. In contrast, allogeneic engineered T-cell therapies can be administered "off-the-shelf" and thus could have immediate availability, improved access, simpler logistics, greater consistency since each batch yields many doses, and flexible dosing, whether through dose titration or re-dosing.

We expect that the cellular engineering strategies that are ultimately successful in immuno-oncology will involve multiple genetic modifications, an application for which we believe CRISPR/Cas9 will play a central role. While other gene editing platforms could potentially be used for these purposes, CRISPR/Cas9 is particularly well-suited for multiplexed editing, which is the modification and/or insertion of multiple genes within a single cell. Gene editing techniques that require different protein enzymes for

each genetic modification may be limited in the number of edits they can make concurrently due to efficiency, cytotoxicity and/or manufacturing challenges. In contrast, CRISPR/Cas9 has the potential to efficiently make multiple edits using a single Cas9 protein and multiple small guide RNA molecules.

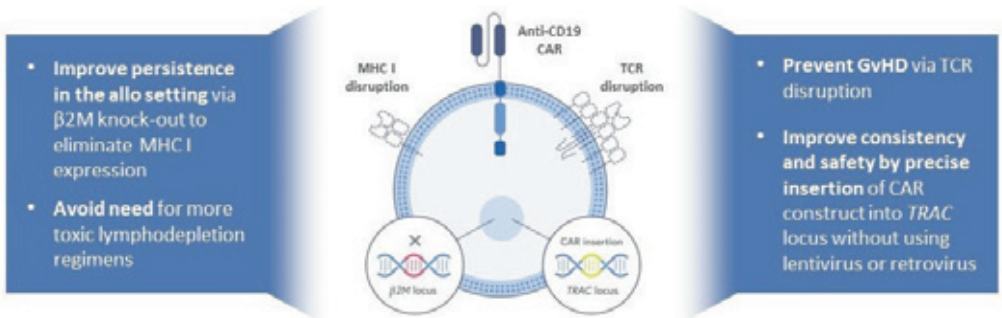
In our immuno-oncology cell therapies, we are using the multiplexing ability of CRISPR/Cas9 both to enable allogeneic administration and to introduce additional genetic edits that aim to improve the efficacy or safety profile of these product candidates. Furthermore, we are leveraging our CRISPR platform to enable a process of continuous innovation in which we incorporate incremental edits into next-generation products to try to increase treatment benefit further. We continue to expand our multiplexing capabilities to help us realize the full potential of engineered cell therapy in immuno-oncology across all tumor types, including solid tumors. Given the important role we believe CRISPR/Cas9 will play in engineered cell therapy going forward we have thus far elected to retain full ownership of our allogeneic CAR T cell programs.

In addition, multiple groups have begun to demonstrate the utility of other immune cells, such as natural killer, or NK, cells, in immuno-oncology therapy. To expand our efforts in gene-edited immune cell therapy beyond T cells, we formed a collaboration with Nkarta that brings together our gene editing technology and cell therapy expertise with Nkarta's leading NK cell discovery, development and manufacturing capabilities. We and Nkarta are co-developing and co-commercializing two donor-derived, gene-edited CAR-NK cell product candidates, one of which targets CD70. Additionally, we are co-developing and co-commercializing a product candidate combining NK and T cells to harness the unique advantages of both cell types.

Our Lead Immuno-Oncology Product Candidate—CTX110

Our lead immuno-oncology product candidate, CTX110, is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting CD19-positive malignancies, such as certain lymphomas and leukemias. A primary aim of CTX110 is to overcome the inefficiency and cost of creating a unique product for each patient with a given tumor type by treating many different patients from a single batch, which we refer to as being an "off-the-shelf" therapy. To generate CTX110, we make three modifications to T cells taken from healthy donors using our gene editing technology: (i) the T-cell receptor, or TCR, is eliminated to reduce the risk of Graft versus Host Disease, or GvHD, from the product candidate, (ii) a CD19-directed CAR is inserted site-specifically into the *TRAC* gene and (iii) the class I major histocompatibility complex, MHC I, is removed from the cell surface in order to improve the persistence of the CAR T cells in an "off-the-shelf" setting. We believe this approach will have advantages over other allogeneic CAR T products in development that semi-randomly insert the CAR using an integrating virus and do not include the MHC I knockout to increase persistence.

CTX110: Differentiated CRISPR-Edited Allogeneic CAR-T Design



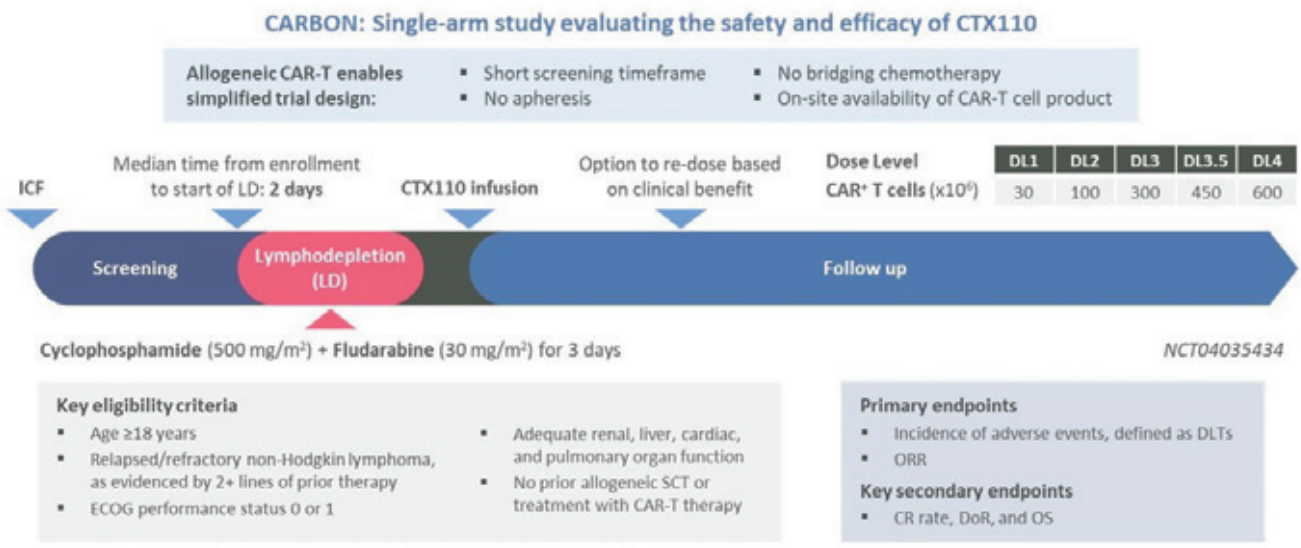
Clinical Trials

We are investigating CTX110 in our CARBON clinical trials, which are designed to assess the safety and efficacy of CTX110 in adult patients with relapsed or refractory CD19-positive B-cell malignancies who have received at least two prior lines of therapy. Based on emerging data from our Phase 1 CARBON clinical trial and discussions with regulatory agencies, we have expanded CARBON to include a Phase 2, potentially registrational, single-arm, multi-center, open-label clinical trial that incorporates consolidation dosing. We have begun dosing patients in this pivotal arm. CTX110 has been granted RMAT designation by the FDA.

The Phase 1 clinical trial is being conducted in two parts – Part A and Part B. In Phase 1 Part A, patients were infused with a single dose of CTX110 ranging from Dose Level (DL) 1 (30 million CAR+ T cells) to DL4 (600 million CAR+ T cells) following a standard lymphodepletion regimen, with an option to re-dose CTX110 based on clinical benefit. In Phase 1 Part B, patients received

CTX110 at DL4 following standard lymphodepletion, as well as a consolidation dose of CTX110 at the same dose level between four and eight weeks after the initial dose for patients that demonstrated clinical benefit.

CARBON Part A Trial Design



In December 2022, at the ASH Annual Meeting, we shared updated clinical data from Phase 1 Part A. As of the October 6, 2022 data cutoff, 32 patients with large B-cell lymphoma, or LBCL, had been treated with CTX110 in Phase 1 Part A and were included in the analysis. All 32 patients had aggressive LBCL, including DLBCL NOS, high grade lymphomas, and tFL. Most patients were refractory to their last line of therapy before entering the trial and 47% of patients had received three or more lines of prior therapy. Patients were infused with a single CTX110 infusion following three days of a standard lymphodepletion regimen consisting of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day). Patients could receive an additional infusion of CTX110 if they achieved initial clinical benefit and subsequently progressed. Additionally, a subset of patients was eligible for a second planned infusion of CTX110 on Day 35.

CARBON Part A Patient Baseline Characteristics

N (%) (unless otherwise noted)	All Dose Levels N=32
Median age, years (range)	64 (25-75)
Female	10 (31)
ECOG performance status at screening	
0	13 (41)
1	19 (59)
Refractory disease	17 (53)
Prior anticancer therapies	
Median prior therapies, n (range)	2 (2-10)
≥3 prior therapies	15 (47)
Prior stem cell transplant	11 (34)
NHL subtype, n (%)	
DLBCL, NOS	17 (53)
High-grade LBCL	5 (16)
Transformed FL	7 (22)
Other*	3 (9)
Baseline SPD >50 cm²	11 (34)
Baseline LDH > ULN	17 (53)

*1 patient in DL1 had Richter's transformation of CLL, 1 patient in DL3 had both Grade 3b follicular lymphoma and germinal center B-cell like-DLBCL, and 1 patient at DL4 had Grade 3b follicular lymphoma

Data cutoff date: 6 October 2022

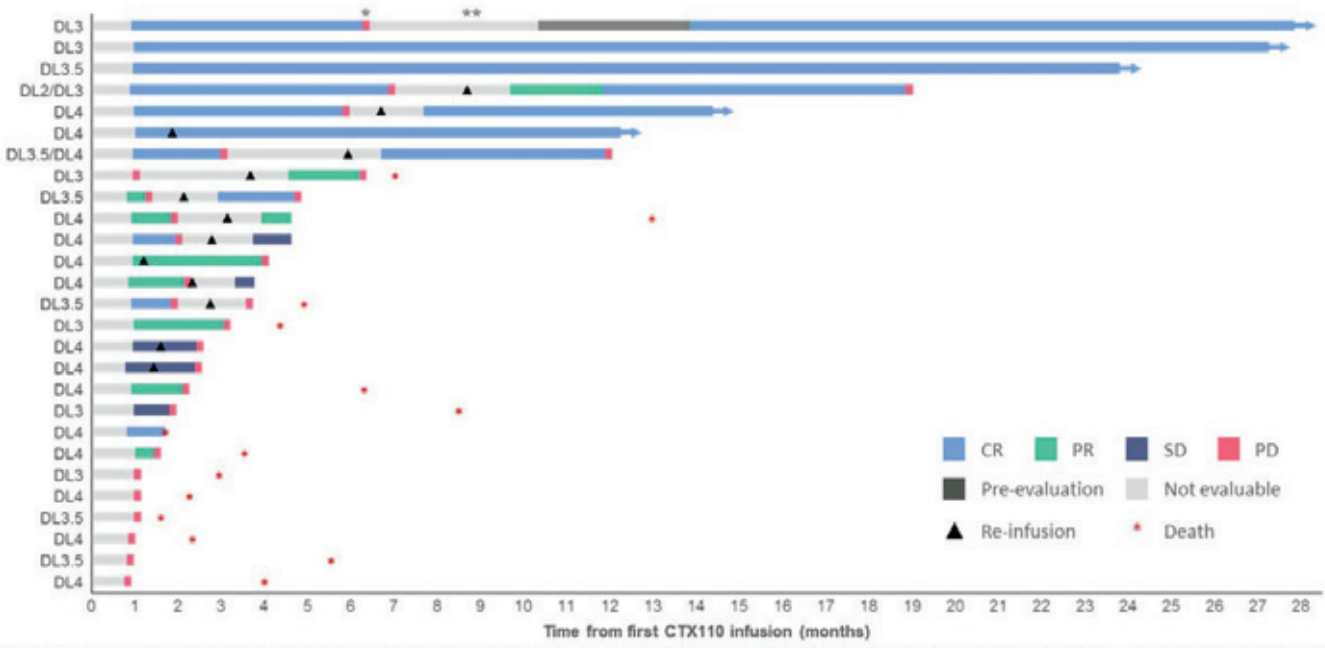
Responses Rates Observed with CTX110 in CARBON Phase 1 Part A

Best response per 2014 Lugano criteria[1]	≥1 infusion at DL≥3* *N=27*
Overall response rate (ORR) N (%)	18 (67%)
Complete response (CR) rate N (%)	11 (41%)

*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3;
(1) Cheson, et al. *J Clin Oncol*. 2014;32(27):3059-68. *Data cutoff date: 6 October 2022*

CTX110 showed encouraging clinical activity in Phase 1 Part A, with a 67% overall response rate, or ORR, and 41% complete response, or CR, rate among patients treated with at least one infusion of CTX110 at DL3 and above (n = 27). Three patients have achieved and maintained a complete response for more than 2 years, demonstrating the potential for CTX110 to produce durable remissions. The six-month CR rate following single infusions of CTX110 at DL3 and above was 19%. Finally, unlike autologous CAR T therapies, almost all enrolled patients received treatment with CTX110, with just 2 of 34 enrolled patients not treated due to intercurrent infections of coronavirus and pneumonia.

Durable Responses Observed with CTX110 in CARBON Phase 1 Part A



*PET CT identified a single new small FDG avid node located in the left upper arm. The lesion was completely excised. The patient remained clinically well and required no subsequent anti cancer therapy inclu steroids, no radiotherapy and no chemotherapy; **On the Month 9 scan, the PET CT identified unspecific localized small FDG uptake in the right upper arm. The patient did not have subsequent surgery nor anticancer therapy, and the lesion spontaneously resolved

CTX110 Was Well Tolerated Across All Dose Levels in CARBON Phase 1 Part A

Adverse events (AEs) of interest, N (%)

	All Dose Levels N=32	
	Gr 1-2	Gr 3+
CRS[1]	18 (56)	-
ICANS[2]	1 (3)	2 (6)
GvHD	-	-
Infections[3]	4 (13)	4 (13)

All events listed in table are treatment-emergent adverse events. CRS and ICANS graded per ASTCT criteria; other adverse events graded per CTCAE
(1) Cytokine Release Syndrome; (2) Immune Effector Cell-associated Neurotoxicity Syndrome; (3) All infections (bacterial, fungal, and viral) included
Data cutoff date: 6 October 2022

CTX110 was well tolerated across all dose levels in Phase 1 Part A. There were no dose-limiting toxicities and no Graft versus Host Disease, or GvHD, or infusion reactions of any grade. All cases of cytokine release syndrome (CRS) were Grade 1 or 2 per the American Society for Transplantation and Cellular Therapy (ASTCT) criteria. Grade 3 or higher infections occurred in 13% of patients, including one patient who died with HHV6 encephalitis and one infection considered possibly related to CTX110. Seven patients experienced serious adverse events attributed to CTX110, which includes CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and febrile neutropenia. Among the 13 patients who received a second infusion of CTX110, there was no change in the overall safety profile.

Emerging data from Phase 1 Part B supports the advancement of CTX110 to a potentially registrational trial. In December 2022, we provided a high-level summary and described this emerging data from Phase 1 Part B and shared our observations as follows: we observed (1) an encouraging efficacy profile with several patients in ongoing complete response beyond six months; (2) clear evidence of the benefits of consolidation dosing, with deepening of complete responses and conversions of stable disease and partial response to ongoing complete responses after the second dose of CTX110; (3) a safety profile consistent with Phase 1 Part A, confirming the tolerability of the consolidation regimen; and (4) peak expansion and overall pharmacokinetics that were comparable between the initial and consolidation doses.

CTX112

In parallel with CTX110, we are advancing CTX112, a next-generation investigational, allogeneic CAR T product candidate targeting CD19. CTX112 includes two additional edits beyond CTX110, leveraging the fact that our CRISPR/Cas9 platform enables us to innovate continuously by incorporating incremental edits into next-generation products. These edits target the genes encoding Regnase-1 and transforming growth factor-beta receptor type 2 (TGFBR2) with the aim of enhancing CAR T potency and reducing CAR T exhaustion. Editing Regnase-1 removes an intrinsic "brake" on T cell function while editing TGFBR2 removes a key extrinsic "brake" on T cell anti-tumor activity. We identified this combination of edits through systematic screening of dozens of novel and previously described genes. Together these edits significantly improve potency in preclinical models, as described for another next-generation investigational program in "*CTX131*." In the fourth quarter of 2022, the IND application for CTX112 was cleared by the FDA.

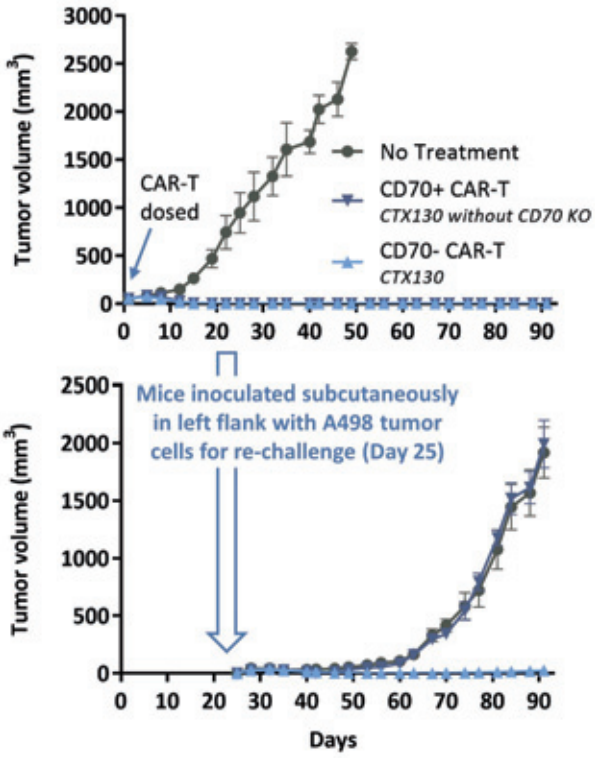
CTX130

An additional immuno-oncology candidate, CTX130, is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting CD70. Several cancers express CD70, including non-Hodgkin's lymphoma, certain T-cell lymphomas, renal cell carcinoma, glioblastoma and pancreatic, lung and ovarian cancers, while normal tissues do not express or show extremely limited expression of CD70. This target enables us to transition from hematological malignancies, such as T-cell lymphoma, to solid tumor cancers, such as renal cell carcinoma.

To generate CTX130, we make the same three modifications used in CTX110 (but with a CAR targeting CD70 rather than CD19), plus add a knockout of the CD70 gene in the T cells to increase CAR T cell function. As shown in the figure below, in preclinical studies, CTX130 eliminated or severely reduced growth of a xenograft model of renal cell carcinoma in all mice treated,

both initially and upon re-challenge. In addition, CTX130 showed improved function over CAR T cells where the CD70 gene remains intact.

Additional edit improved the performance of CTX130 against a subcutaneous A498 renal cell carcinoma model

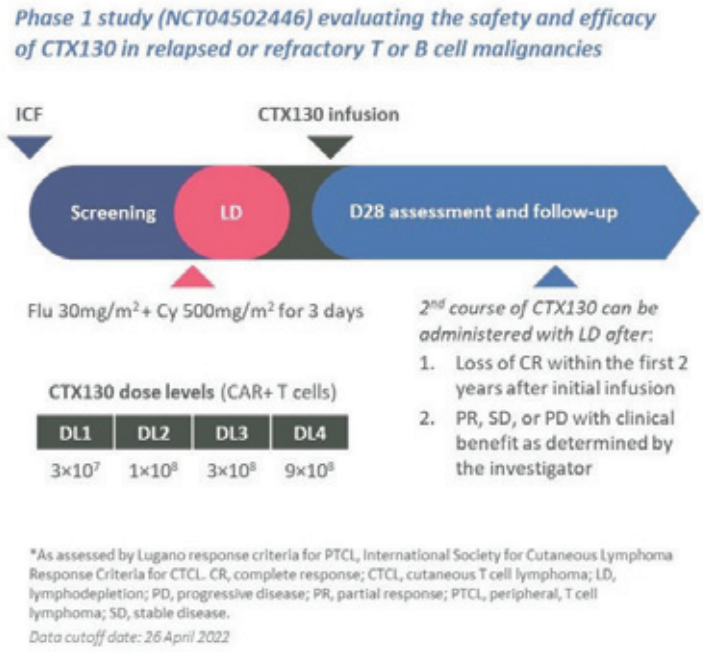


Clinical Trials

We are currently investigating CTX130 in two ongoing independent Phase 1, single-arm, multi-center, open-label clinical trials, COBALT-LYM and COBALT-RCC, that are designed to assess the safety and efficacy of several dose levels of CTX130 in adult patients. CTX130 has received Orphan Drug Designation from the FDA for the treatment of T cell lymphoma and RMAT designation for the treatment of Mycosis Fungoides and Sézary Syndrome (MF/SS).

The COBALT-LYM trial is designed to evaluate the safety and efficacy of CTX130 in adult patients with relapsed or refractory T or B cell malignancies. Dose escalation of CTX130 was performed in adult patients with relapsed or refractory T cell lymphoma with at least 10% expression of CD70. Given the inherent difficulties and potential risks of manufacturing a CAR T therapy from a patient's own diseased T cells, allogeneic cellular therapy approaches for T cell lymphoma have greater potential to address the unmet need in this patient population. Patients in COBALT-LYM received three days of a standard lymphodepletion regimen consisting of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day), followed by a single infusion of CTX130. Patients who showed clinical benefit from the first CTX130 infusion were eligible to be re-dosed following disease progression. The primary endpoints include safety as measured by the incidence of dose-limiting toxicities and ORR. Key secondary endpoints include progression free survival and overall survival.

COBALT-LYM Trial Design



In June 2022, at the EHA Congress, we shared initial clinical data from COBALT-LYM. As of the April 26, 2022, data cutoff, 19 patients with T cell malignancies had been enrolled, of which 18 patients had received CTX130 with at least 28 days of follow-up and were included in the analysis. Prior to enrollment, all patients were heavily pre-treated, with a median of four systemic therapies. Additionally, all patients were refractory to their last line of therapy. Eight patients had peripheral T-cell lymphoma (PTCL) and 10 patients had cutaneous T-cell lymphoma (CTCL).

Clinically meaningful responses were observed with CTX130, with a higher percentage of patients responding at higher dose levels. Disease assessment was performed by investigator review according to the 2014 Lugano Response Criteria for PTCL or the International Society for Cutaneous Lymphoma Response Criteria (Olsen criteria) for CTCL, as appropriate. At DL3 and above, the ORR was 70% and the CR rate was 30%. In addition, 90% of patients at DL3 and above had clinical benefit, defined as a stable disease or better. Median CD70 expression among the patients was 90%, but responses were observed across all levels of CD70 expression. Responses were largely consistent in both PTCL and CTCL, with ORRs of 80% and 60%, respectively, at DL3 and above. Broad activity and deep responses were seen in all disease compartments, including the lymph nodes, skin and blood, in patients with CTCL following treatment with CTX130.

Responses Rates Observed with CTX130 in COBALT-LYM

Best overall response, n (%)

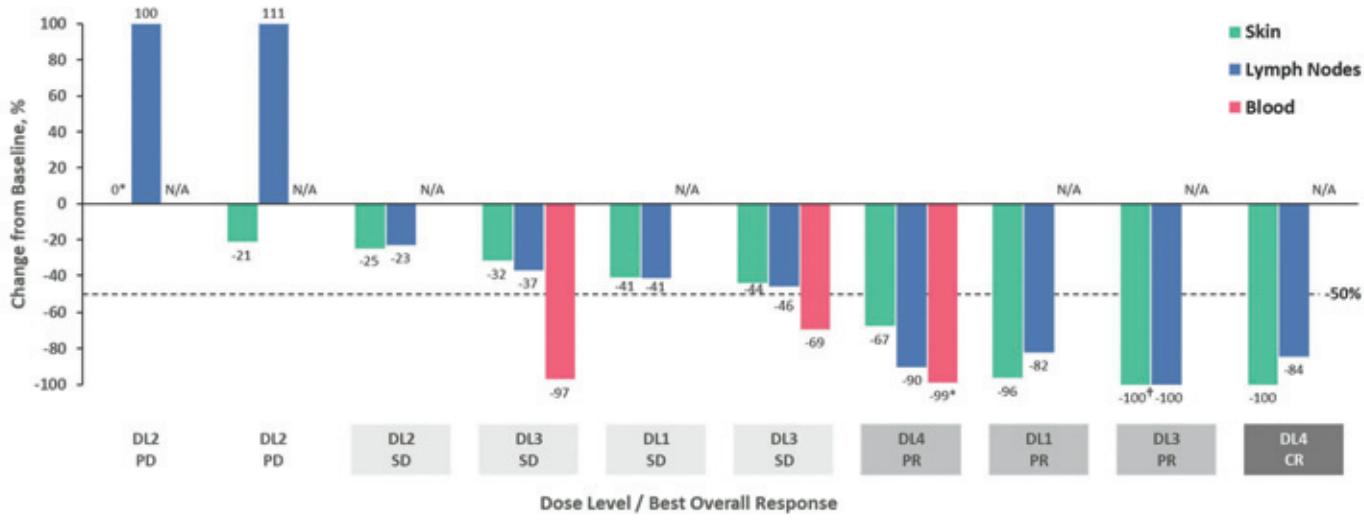
Cell dose (CAR+ T cells)	DL1 $3x10^7$ N=4	DL2 $1x10^8$ N=4	DL3 $3x10^8$ N=5	DL4 $9x10^8$ N=5	DL≥3 N=10
Overall Response Rate (ORR)	2 (50)	0	3 (60)	4 (80)	7 (70)
CR	1 (25)	0	2 (40)*	1 (20)	3 (30)
PR	1 (25)	0	1 (20)	3 (60)	4 (40)
Disease Control Rate (DCR = CR + PR + SD)	3 (75)	1 (25)	5 (100)	4 (80)	9 (90)

	PTCL		CTCL	
	DL≥3 N=5	Total N=8	DL≥3 N=5	Total N=10
ORR	4 (80)	5 (63)	3 (60)	4 (40)
CR	2 (40)	3 (38)	1 (20)	1 (10)
PR	2 (40)	2 (25)	2 (40)	3 (30)
DCR	4 (80)	5 (63)	5 (100)	8 (80)

*1 patient in DL3 who initially achieved a PR was re-infused at DL4 following a change to SD and achieved a CR at DL4. CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; DCR, disease control rate; DL, dose level; ORR, overall response rate; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease

Data cutoff date: 26 April 2022

Responses Observed Across All Compartments in CTCL



*Day 7 assessment; †Initially unconfirmed CR, later confirmed to be PR by mSWAT and biopsy.
CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; SD, stable disease

Data cutoff date: 26 April 2022

CTX130 was well tolerated across all dose levels. There were no cases of GvHD, no dose-limiting toxicities, and no instances of tumor lysis syndrome (TLS). All cases of CRS and ICANS were Grade 1 or 2 per the ASTCT criteria and either required no specific intervention or resolved following standard CRS management. Neither the frequency nor severity of CRS has increased in patients who were re-dosed with CTX130. There was a sudden death in one patient with William's syndrome in the context of a lung infection, deemed unrelated to CTX130. There were no treatment related deaths in the trial.

CTX130 Was Well Tolerated Across All Dose Levels in COBALT-LYM

Adverse Events of Interest, N (%)

	DL1 $3x10^7$ N=4		DL2 $1x10^8$ N=4		DL3 $3x10^8$ N=5		DL4 $9x10^8$ N=5		DL≥3 N=10	
	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3
CRS	1 (25)	-	1 (25)	-	4 (80)	-	4 (80)	-	**8 (80)**	-
ICANS	-	-	-	-	3 (60)	-	-	-	**3 (30)**	-
GvHD	-	-	-	-	-	-	-	-	-	-
Infections	2 (50)	1 (25)	-	1 (25)	2 (40)	1 (20)	1 (20)	1 (20)	**3 (30)**	**2 (20)**

All events listed in table are treatment-emergent adverse events.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; GvHD, graft versus host disease; ICANS, immune effector cell associated neurotoxicity syndrome

Data cutoff date: 26 April 2022

In addition to COBALT-LYM, CTX130 is also being evaluated in the COBALT-RCC trial, which is designed to evaluate the safety and efficacy of CTX130 for the treatment of relapsed or refractory renal cell carcinoma. Dose escalation of CTX130 was performed in adult patients with unresectable or metastatic renal cell carcinoma with clear cell differentiation. As with COBALT-LYM, patients received three days of a standard lymphodepletion regimen consisting of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day), followed by a single infusion of CTX130. Patients who demonstrated a response from the first CTX130 infusion could be re-dosed upon disease progression, and those demonstrating clinical benefit in the presence of stable or progressive disease could also receive re-dosing. The primary endpoints include safety as measured by the incidence of dose-limiting toxicities and ORR. Key secondary endpoints include best overall response, progression free survival and overall survival.

In November 2022, at the Society of Immunotherapy in Cancer Annual Meeting, we shared preliminary clinical data from COBALT-RCC. As of the May 2, 2022 data cutoff, 14 patients with stage IV clear cell renal cell carcinoma had been enrolled, of which all patients had received CTX130 and were included in the safety analysis, while 13 patients were evaluated for efficacy. Prior to enrollment, all patients were heavily pre-treated, with a median of three systemic therapies.

CTX130 showed encouraging antitumor activity in COBALT-RCC. One patient experienced a durable complete response, the first to be achieved with allogeneic CAR T cell therapy in patients with relapsed/refractory solid tumors. This patient remained in ongoing complete response through Month 18 at the time of data cutoff. Overall, CTX130 achieved a 77% disease control rate, with nine patients achieving stable disease, in a heavily pretreated renal cell carcinoma patient population. The longest duration of stable disease achieved was observed for 7.8 months and was ongoing at the time of data cutoff. During periods of stable disease, patients did not receive any other anticancer therapies. CTX130 demonstrated typical pharmacokinetics, with peak expansion occurring at a median of Day 10.

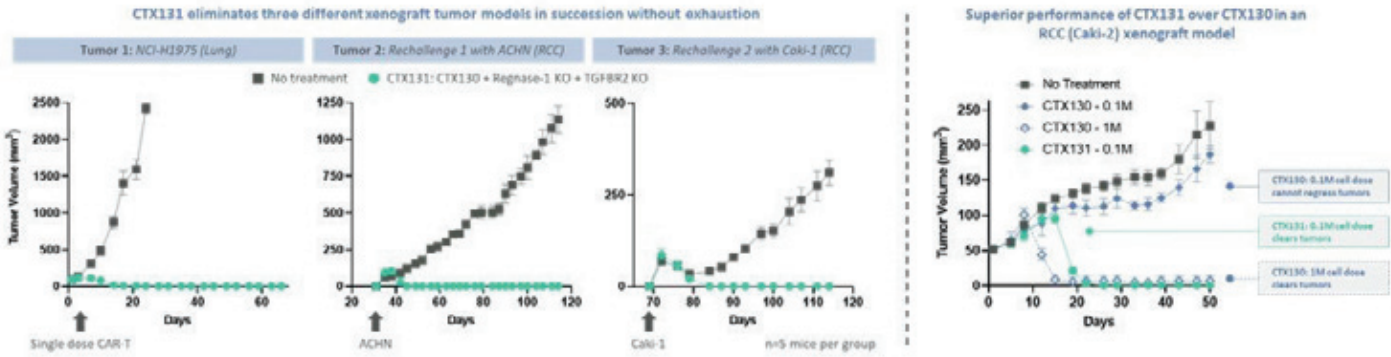
CTX130 was well tolerated across all dose levels. There were no cases of GvHD, no dose-limiting toxicities, no instances of ICANS, and no instances of TLS. All cases of CRS were Grade 1 or 2 per the ASTCT criteria and either required no specific intervention or resolved following standard CRS management. Neither the frequency nor severity of CRS has increased in patients who were re-dosed with CTX130. Three patients had SAEs of infections, all unrelated to CTX130, including Grade 5 pneumonia with Grade 4 dyspnea resulting in the death of one patient. There were no treatment-related deaths in the trial.

This first-in-human clinical trial exploring CD70-targeting CAR T cell therapy in clear cell renal cell carcinoma showed a tolerable safety profile with no off-target toxicities and encouraging antitumor activity. These preliminary results from the COBALT-RCC study represent a clinically meaningful proof-of-concept for further exploration of CD70-targeting CAR T cells in renal cell carcinoma and other CD70-positive malignancies and underscore the potential of further increasing potency.

CTX131

In parallel with CTX130, we are advancing CTX131, a next-generation investigational, allogeneic CAR T product candidate targeting CD70 for the potential treatment of both solid tumors and certain hematologic malignancies. CTX131 includes two additional edits beyond CTX130. These edits, the same used in CTX112, target the genes encoding Regnase-1 and TGFBR2, with the aim of enhancing CAR T potency and reducing CAR T exhaustion. Together these edits synergistically improve potency approximately 10-fold in preclinical models, as shown below. In the first quarter of 2023, the IND for CTX131 was cleared by the FDA.

CTX131 Shows Enhanced Potency, with the Regnase-1 and TGFBR2 Edits Increasing Potency Approximately 10-fold



Regenerative Medicine

Regenerative medicine, or the use of stem cells to repair or replace tissue or organ function lost due to disease, damage or age, holds potential to treat both rare and common diseases. The field is approaching the point where clinical proofs of concept have begun to emerge. Most of these efforts use unmodified stem cells, and the potential to genetically engineer these cells via gene editing is large. We are pursuing allogeneic stem cell-derived therapies using CRISPR/Cas9 gene editing to enable immune evasion, improve cell function, and direct cell fate. Our first major effort in this area is in diabetes and we and ViaCyte, are advancing a series of programs as part of a strategic collaboration for the discovery, development, and commercialization of gene-edited stem cell therapies for the treatment of diabetes.

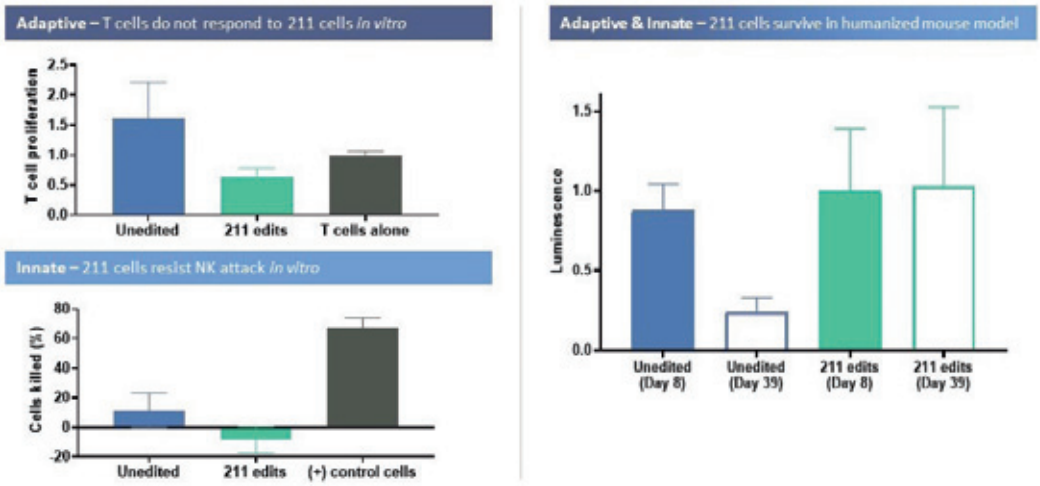
ViaCyte Collaboration in Diabetes

Clinical data with islet transplants indicate that beta-cell replacement approaches may offer benefit to patients with insulin-requiring diabetes. ViaCyte has pioneered the approach of generating pancreatic-lineage cells from stem cells and delivering them safely and efficiently to patients. ViaCyte previously evaluated an unedited product candidate using a non-immunoprotective delivery device that permits direct vascularization of the cell therapy. Encouragingly, clinical proof-of-concept data with this earlier product candidate showed that the cell therapy could produce insulin in people with T1D. However, because a patient's immune system will identify these cells as foreign, patients would require long-term immunosuppression to avoid rejection.

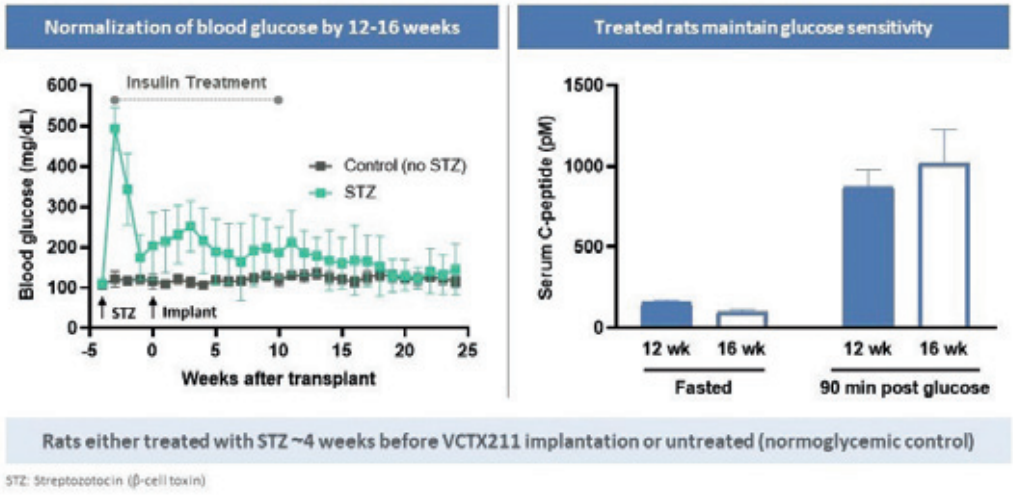
Our gene editing technology offers the potential to protect the transplanted cells from the patient's immune system by *ex vivo* editing of immuno-modulatory genes within the stem cell line used to produce the pancreatic-lineage cells. We believe that the speed, specificity and multiplexing efficiency of CRISPR/Cas9 make our technology well suited to this task. In addition, our CRISPR platform enables a process of continuous innovation, with incremental edits incorporated into next-generation product candidates with the aim of increasing treatment benefit further.

This feature of the CRISPR/Cas9 platform has led us to pursue a multi-staged product strategy. Our initial product candidate, VCTX210, is an investigational, allogeneic, gene-edited, immune-evasive, stem cell-derived product candidate for the treatment of T1D developed by applying our gene editing technology to ViaCyte's proprietary stem cell capabilities. VCTX210 incorporates four gene edits designed to promote immune evasion and cell fitness: knock-out of B2M and TXNIP and knock-in of PD-L1 and HLA-E. We and ViaCyte are investigating VCTX210 in an ongoing Phase 1 clinical trial that is designed to assess VCTX210's safety, tolerability, and immune evasion in patients with T1D, and are in the follow-up stage for this clinical trial. Our next investigational product candidate, VCTX211, incorporates two additional gene edits beyond those in VCTX210 that aim to enhance cell fitness further: knock-in of both MANF and A20 to improve graft acceptance and beta cell proliferation and provide protection from cytokine induced apoptosis. Collectively, these edits improve the ability of beta cells to evade the immune system *in vitro* and *in vivo* in preclinical models, as shown below. In addition, VCTX211 has been shown to reverse hyperglycemia in a diabetic rat model. In the fourth quarter of 2022, the Clinical Trial Application for VCTX211 was cleared by Health Canada and the Phase 1/2 clinical trial is ongoing.

VCTX211 Cells Evade Immunity *In Vitro* and *In Vivo*



VCTX211 Reverses Hyperglycemia in a Diabetic Rat Model



In Vivo Approaches

We believe that *in vivo* gene editing, or delivery of a CRISPR/Cas9-based therapeutic directly to tissues within the human body, has reached a threshold for clinical translation. As a result, we have established a leading platform for *in vivo* gene editing in the liver and are rapidly advancing a broad portfolio of *in vivo* programs for both rare and common diseases towards clinical trials. Our lead *in vivo* programs target the liver to take advantage of clinically established and validated delivery technologies, principally LNPs, that are now available. LNPs have several advantages that make them well-suited for delivering CRISPR/Cas9 *in vivo*, including efficient and safe delivery to the liver, large cargo size and transient cargo expression. Within the liver, we are pursuing diseases that are amenable to a gene disruption strategy and have well-understood genetic linkages, such as cardiovascular disease via genetic targets like *ANGPTL3*, *LPA*, and *PCSK9*. We believe this approach of leveraging existing proofs of concept reduces the challenges associated with delivering CRISPR/Cas9-based therapeutics *in vivo*.

Beyond the liver, for delivery to hematopoietic stem cells, the central nervous system, and other extrahepatic tissues, we are pursuing additional delivery technologies, including adeno-associated virus (AAV) vectors and further advancements to nanoparticle technology. Through internal efforts and external collaborations, we are developing new delivery modalities to support future *in vivo* therapeutics.

Cardiovascular and Dyslipidemia Programs

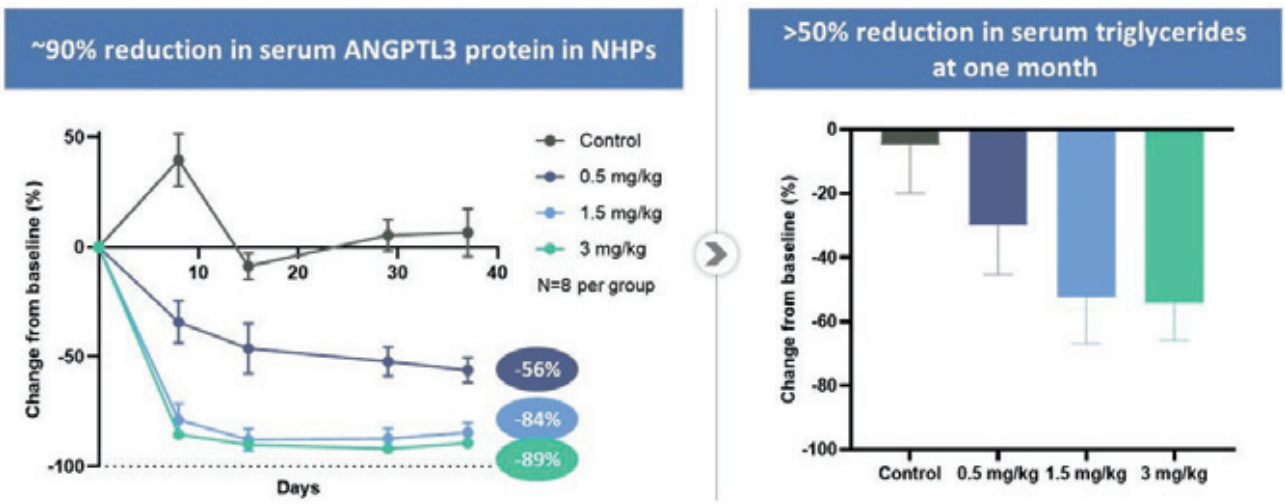
Cardiovascular disease (CVD) is the leading cause of death globally, accounting for over 30% of all deaths, or nearly 18 million people, in 2019. CVD includes heart failure, stroke, atherosclerotic cardiovascular disease (ASCVD), aortic valve calcification and more. Dyslipidemias are a leading cause of CVD. Dyslipidemias are characterized by abnormally high levels of lipids, including cholesterol, lipoproteins and triglycerides, in the blood stream. Three of the most common dyslipidemias are hypercholesterolemia, hypertriglyceridemia and elevated lipoprotein(a), or Lp(a).

We are developing *in vivo* editing therapies to treat CVD by lowering levels of key lipids like low density lipoprotein (LDL)-cholesterol (LDL-C), triglycerides and Lp(a). We have chosen to pursue this area given: (1) proven benefit based on natural human genetics and antibody and RNA therapeutics; (2) the opportunity to shift the treatment paradigm with a single-dose, potentially lifetime durable editing approach; (3) the ability to use development paths starting with severe disease and expanding to much larger patient populations; and (4) the potential for combination therapy across programs.

CTX310 – ANGPTL3

Our lead investigational *in vivo* program, CTX310, for which we are currently conducting IND-enabling studies, targets the gene encoding angiopoietin-related protein 3 (ANGPTL3) for the treatment and prevention of CVD. ANGPTL3 plays an important role in lipid metabolism by inhibiting an enzyme called lipoprotein lipase (LPL). LPL is the main enzyme that breaks down triglyceride-enriched lipoproteins like chylomicrons, very low density lipoprotein (VLDL) and LDL. By preventing LPL from hydrolyzing these lipoproteins, ANGPTL3 activity increases the level of circulating triglycerides. Reducing ANGPTL3 expression by disrupting the *ANGPTL3* gene increases LPL expression and thereby reduces triglyceride-rich lipoproteins, as well as LDL-C. This mechanism has been validated through natural history studies, as individuals with natural loss-of-function variants of ANGPTL3 have lower triglyceride levels, lower LDL-C levels, and a lower risk of coronary artery disease. CTX310, which consists of messenger RNA encoding Cas9 and a guide RNA targeting ANGPTL3 delivered via LNP, aims to recapitulate this effect by disrupting the ANGPTL3 gene. CTX310 has been shown to decrease ANGPTL3 protein levels by nearly 90% in non-human primates (NHPs), leading to a greater than 50% reduction in serum triglycerides.

Approximately 90% reduction in serum ANGPTL3 protein resulting in >50% reduction in serum triglycerides in NHPs following treatment with CTX310



CTX320 – Lp(a)

Our second investigational *in vivo* program, CTX320, targets another protein associated with CVD: Lp(a). Lp(a) is a lipoprotein consisting of an LDL-like particle covalently bound to a protein called apolipoprotein(a), or apo(a). Lp(a) transports cholesterol in the blood and is highly atherogenic. It can infiltrate and bind to components of the extracellular matrix in the inner layers of the aortic valve and other areas of the circulatory system, resulting in increases in inflammation and fatty deposits that over time lead to a weakened aortic valve and other serious symptoms contributing to CVD. Lp(a) is its own independent risk factor for CVD. High concentrations of Lp(a), as well as genetic variants associated with high Lp(a) concentrations, are both associated with CVD. Elevated levels of Lp(a) above 50 mg/dL are directly associated with aortic valve calcification disease (AVCD). Up to 20% of adults in the United States have Lp(a) levels above 50 mg/dL and over 1 million adults in the United States have AVCD. Additionally, 30% of patients with familial hypercholesterolemia have elevated Lp(a) levels. To date, there are no Lp(a) lowering therapies approved by the

FDA. CTX320 consists of a guide RNA targeting *LPA*, the gene encoding apo(a), and messenger RNA encoding Cas9 delivered via LNP. By reducing levels of apo(a), CTX320 should reduce plasma levels of Lp(a) substantially, as supported by preclinical data showing that treatment with CTX320 decreases Lp(a) levels by over 90% in NHPs.

Hypercholesterolemia

Hypercholesterolemia is defined by levels of LDL-C, also known as "bad cholesterol," above 130 mg/dL and is associated with increased risk of heart disease and stroke. In hypercholesterolemia, high levels of LDL-C accumulate in blood vessels, leading to atherosclerosis. Treatment aims to reduce LDL-C levels to below 100 mg/dL with 70 mg/dL as the ultimate goal, but some patients cannot achieve this level of reduction through existing means. Patients with LDL-C levels above 200 mg/dL are considered to have familial hypercholesterolemia (FH). Patients with FH have one or more genetic mutations that contribute to the disease in addition to diet and lifestyle. Patients with FH cannot metabolize LDL-C effectively, leading to high levels of circulating LDL-C, in some cases exceeding 1000 mg/dL. FH can be subcategorized by mutation status into heterozygous and homozygous familial hypercholesterolemia (HeFH and HoFH). HoFH patients have the most severe phenotype, with LDL-C levels usually exceeding 400 mg/dL. HoFH patients often suffer from CVD early in life and have an average life expectancy of 33 years if untreated. HoFH has a prevalence of 1 in 200,000 to 1,000,000 adults.

Hypertriglyceridemia

Hypertriglyceridemia is clinically defined as having triglyceride levels above l50 mg/dL. The most severe patients can have levels exceeding 2000 mg/dl. Hypertriglyceridemia is associated with CVD and acute pancreatitis. Like LDL-C, triglyceride levels can be affected by diet and lifestyle choices and treated with common therapies. However, over three million adults in the United States still have severe hypertriglyceridemia (sHTG). Known genetic conditions can cause sHTG, including familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS). There are parallels between FCS/MCS and HoFH/HeFH. FCS is the only true monogenic form of hypertriglyceridemia and is associated with extreme levels of triglycerides exceeding 885 mg/dL. The prevalence of FCS is 1 in 200,000 to 300,000 individuals in the United States and EU. MCS is polygenic in nature, meaning that the genetic underpinnings causing the disease vary among individuals, and is clinically defined as having triglyceride levels between 150 and 885 mg/dL. MCS has a prevalence of 1 in 600 to 1,000 individuals.

Additional In Vivo Programs

Building upon CTX310 and CTX320, we have a number of earlier stage investigational *in vivo* programs leveraging gene disruption in the liver for both rare and common diseases. These include CTX330, which targets *PCSK9*, a well understood target for CVD with robust data from natural human genetics and other therapeutic modalities. In addition, we have programs focused on gene correction in the liver, including for hemophilia A. Beyond the liver, we have programs targeting hematopoietic stem cells, the central nervous system, and other tissues. For instance, in collaboration with Capsida, we are developing *in vivo* gene editing therapies for the treatment of amyotrophic lateral sclerosis (ALS) and Friedreich's ataxia. Capsida's high-throughput AAV engineering platform aims to generate capsids optimized to target specific tissue types and limits transduction of tissues and cell types not relevant to the target disease, potentially improving the activity and tolerability of our gene editing investigational therapies. The combination of our technologies could thereby enable best-in-class therapies for these devastating neurodegenerative diseases.

Hemophilia A

Hemophilia A is a rare, typically X-linked, recessive bleeding disorder caused by insufficient or nonfunctioning coagulation protein, factor VIII (FVIII). Hemophilia A is the most common type of hemophilia disorder comprising 80-85% of the total hemophilia population and accounting for 900,000 people worldwide, including 1 in every 4-10,000 male births. In patients with hemophilia A, lack of effective clotting due to deficient functional FVIII activity may present in patients as: easy bruising and swelling, prolonged bleeding after injuries, surgeries, or recurrent bleeding prior to wound healing and, in moderate and severe hemophilia, spontaneous hemorrhage.

Severity of disease has traditionally been defined based on the residual amount of FVIII in the blood with mild defined as >5-40%, moderate as 1-5%, and severe as <1%. Normal values for FVIII are between 50-150%. Individuals with severe hemophilia A are typically diagnosed within the first two years of life. Without prophylactic treatment, patients suffering severe disease may average up to two to five spontaneous bleeding episodes per month, including joint bleeding and deep muscle hematomas. Patients with moderate disease are usually diagnosed by age five and have spontaneous bleeding at a rate of once a month to once a year and suffer from prolonged bleeding after injuries. Individuals with mild disease are diagnosed later in life and do not have spontaneous bleeding but exhibit abnormal bleeding after surgeries and other procedures.

Current standard of care for hemophilia A includes the use of plasma-derived or recombinant clotting factor concentrate to prevent uncontrolled bleeding. Several gene therapies are being investigated in clinical trials, most of which aim to deliver a functional copy of the *F8* gene into target cells using AAV vectors. One of these gene therapies, Roctavian, received conditional approval by the EMA in August 2022. However, because AAV vectors do not integrate into a patient's genome, transduced cells may lose episomal AAV as they divide, leading to declining FVIII levels and waning therapeutic benefit. In addition, the immunogenic

nature of AAV vectors means that in most cases patients cannot receive additional infusions of the therapy. In contrast, we are developing a gene-edited product candidate to treat hemophilia A that uses CRISPR/Cas9 to insert a functional *F8* gene into a specific location in a patient's genome. This approach is intended as a one-time curative therapy where direct insertion of the *F8* gene will lead to lifelong production of functional FVIII protein.

CRISPR-X: Further Unlocking the Potential of Our Gene Editing Platform

While we have made significant progress with our current portfolio of programs, we recognize that we need to continue to innovate to unlock the full potential of CRISPR gene editing and bring transformative therapies to even more patients. In 2022, we launched a new early-stage research team known as CRISPR-X that focuses on innovative research to develop next-generation gene editing modalities. CRISPR-X focuses on technologies to enable whole gene correction and insertion without requiring homology-directed repair, which occurs at low efficiency in many cells, or viral delivery of a DNA template, which creates toxicity risks and technical challenges. These technologies include all-RNA gene correction, non-viral delivery of DNA and novel editing and insertion techniques. These efforts complement our existing platform capabilities, such as guide RNA selection, on- and off-target assessment and multiplexing.

Vertex Partnered Programs

We have partnered certain of our programs in other disease areas, such as Duchenne muscular dystrophy, or DMD, myotonic dystrophy type 1, or DM1, and cystic fibrosis, or CF. We have entered into collaboration agreements with respect to these three programs with Vertex, a global leader in rare diseases with extensive disease area expertise in CF, and we retain the option to co-develop and co-commercialize products for the treatment of DM1. We believe that our CRISPR/Cas9 gene editing technology is well suited to address DMD, DM1 and CF, all of which have significant patient populations with high unmet medical need.

Duchenne Muscular Dystrophy (DMD)

DMD is an X-linked recessive genetic disease caused by mutations in the dystrophin gene, which results in a lack of the dystrophin protein. Because dystrophin plays a key structural role in muscle fiber function, the absence of this protein in muscle cells leads to significant cell damage and ultimately causes muscle cell death and fibrosis. Patients with the disease experience muscle degeneration, loss of mobility and premature death. DMD is among the most prevalent severe genetic diseases, occurring in one in 3,300 male births worldwide. There are currently two approved disease-modifying therapies in the United States for the treatment of DMD, one for patients who have confirmed mutations of the dystrophin gene amenable to exon 51 skipping and one for patients who have confirmed mutations of the dystrophin gene amenable to exon 53 skipping. These mutations affect about 13% and 8% of the DMD population, respectively.

Myotonic dystrophy type 1 (DM1)

DM1 is an autosomal genetic disease caused by the expansion of a CTG trinucleotide repeat in the noncoding region of the *DMPK* gene. The disease affects the skeletal and smooth muscle, as well as other organ systems, such as the eye, heart, endocrine system, and central nervous system. The clinical manifestations of DM1 span a continuum from mild to severe. Based on these phenotypes, DM1 is classified into three somewhat overlapping forms: mild, classic, and congenital. Patients with mild DM1 have normal lifespans and typically develop cataracts, and experience mild sustained muscle contractions, or myotonia. Those with classic DM1 tend to have muscle weakness and wasting, myotonia, cataracts and often abnormalities in cardiac conduction, and may become physically disabled and have shortened lifespans. Patients with congenital DM1 commonly have intellectual disability and typically have hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death. DM1 affects around 1 in 8,000 people worldwide. No approved therapies exist to treat the underlying disease; instead, most interventions to date aim to address specific symptoms of the disease.

Cystic Fibrosis (CF)

CF is a progressive disease caused by mutations in the cystic fibrosis transmembrane regulator, or CFTR, gene resulting in the loss or reduced function of the CFTR protein. Patients with CF develop thick mucus in vital organs, particularly in the lungs, pancreas and gastrointestinal tract. As a result, CF patients experience chronic severe respiratory infections, chronic lung inflammation, poor absorption of nutrients, progressive respiratory failure and early mortality. The median age of death from CF in the United States was 31 years in 2017, with most deaths resulting from respiratory failure. CF is an orphan disease that is estimated to affect more than 70,000 patients in the United States and Europe. CF patients require lifelong treatment with multiple daily medications and hours of self-care. They often require frequent hospitalizations and sometimes even lung transplantation, which can prolong survival but is not curative.

Bayer Partnered Programs

We are also investigating programs for the diagnosis, treatment, or prevention of certain autoimmune disorders and eye disorders. For these and the program for hemophilia A disorders described above, Bayer has options to either co-develop and co-commercialize two products with us or, under certain circumstances, exclusively license such optioned products.

Strategic Partnerships and Collaborations

We intend to develop CRISPR/Cas9-based therapeutics both independently and in collaboration with current and potential future corporate partners. We view strategic partnerships as a core component of our strategy, allowing us to access capabilities and resources in support of our therapeutic programs. We maintain broad strategic partnerships to develop gene editing-based therapeutics in specific disease areas.

Vertex

We have entered into a series of agreements with Vertex that contemplate certain research, development, manufacturing and commercialization activities involving various targets. Since October 2015, we have entered into a Strategic Collaboration, Option and License Agreement, as amended in 2017 and 2019, or the 2015 Collaboration Agreement; a Joint Development and Commercialization Agreement, or the Vertex JDA, which was amended and restated in April 2021, or the A&R Vertex JDCA; and a Strategic Collaboration and License Agreement, as amended in April 2021, or the 2019 Collaboration Agreement.

2015 Collaboration Agreement

Pursuant to the 2015 Collaboration Agreement, we agreed to provide technology and options to obtain licenses relating to our CRISPR/Cas technology to Vertex in exchange for a $75.0 million upfront payment. In 2015, in connection with the initial entry into the 2015 Collaboration Agreement, Vertex also made a $30.0 million equity investment in us.

The initial focus of the 2015 Vertex collaboration was to use CRISPR/Cas9 technology to discover and develop gene-based treatments for hemoglobinopathies and cystic fibrosis. In 2017, Vertex exercised its option to co-develop and co-commercialize the hemoglobinopathies program. Matters relating to hemoglobinopathies targets are governed by the A&R Vertex JDCA, as summarized below. Further discovery efforts focused on a specified number of other genetic targets. Under the 2015 Collaboration Agreement, Vertex had the option to exclusively license treatments for a specified number of collaboration targets that emerged from the four-year research collaboration under certain of our platform and background intellectual property to develop, manufacture, commercialize, sell and use therapeutics directed to each such collaboration target. We were responsible for discovery activities, and the related expenses were fully funded by Vertex.

In October 2019, Vertex exercised the remaining options granted to it under the 2015 Collaboration Agreement to exclusively in-license three additional targets for the development of gene-based treatments using CRISPR-based gene editing. The targets include the cystic fibrosis transmembrane conductance regulator gene and two undisclosed targets. Under the terms of the 2015 Collaboration Agreement, we received an upfront payment of $30.0 million in connection with the option exercise and have the potential to receive up to $410.0 million in development, regulatory and commercial milestones, as well as royalty payments in the single digits to low teens on net product sales for each of the three targets. The milestone and royalty payments are each subject to reduction under certain specified conditions set forth in the 2015 Collaboration Agreement. For these targets, Vertex is solely responsible for all research, development, manufacturing and global commercialization activities and Vertex received exclusive rights to develop and commercialize products related to these targets globally. The research term of the 2015 Collaboration Agreement has expired, and Vertex no longer holds rights to in-license additional targets under the 2015 Collaboration Agreement.

Either party can terminate the 2015 Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. Vertex also has the right to terminate the 2015 Collaboration Agreement for convenience at any time upon 90 days' written notice prior to any product receiving marketing approval and upon 270 days' notice after a product has received marketing approval. We may also terminate the 2015 Collaboration Agreement in the event Vertex challenges any of our patent rights.

Absent early termination, the 2015 Collaboration Agreement will continue until the expiration of the Vertex's payment obligations under the 2015 Collaboration Agreement.

Joint Development Agreement

In December 2017, we entered into the Vertex JDA with Vertex pursuant to which the parties agreed to, among other things, co-develop and co-commercialize exa-cel and other product candidates specified in the Vertex JDA. In April 2021, we and Vertex agreed to amend and restate the Vertex JDA and entered into the A&R Vertex JDCA, pursuant to which the parties agreed to, among other things, (a) adjust the governance structure for the collaboration and adjust the responsibilities of each party thereunder; (b) adjust the allocation of net profits and net losses between the parties with respect to exa-cel only; and (c) exclusively license (subject to our

reserved rights to conduct certain activities) certain intellectual property rights to Vertex relating to the specified product candidates and products (including exa-cel) that may be researched, developed, manufactured and commercialized under such agreement.

The A&R Vertex JDCA includes, among other things, provisions relating to the following:

Governance; Activities. We and Vertex disbanded the previously established collaboration strategy team and all working groups established by such team and established the following committees: (i) a joint oversight committee to provide high-level oversight and (ii) a transition committee to provide for forum planning, discussing and sharing information regarding certain transition activities until completion of such activities. Each of the new committees contain an equal number of representatives from each of CRISPR and Vertex. The A&R Vertex JDCA provides that, subject to the terms and conditions of such agreement, Vertex has the right to conduct all research, development, manufacturing and commercialization activities relating to the specified product candidates and products (including exa-cel) throughout the world subject to our reserved right to conduct certain activities. We will continue to participate in certain aspects of such activities in an observer capacity unless and to the extent otherwise agreed to by the parties.

Financial Terms. In the second quarter of 2021, in connection with the closing of the transaction contemplated by the A&R Vertex JDCA, we received a $900 million up-front payment from Vertex. Additionally, we are eligible to receive a one-time $200 million milestone payment upon receipt by Vertex of the first marketing approval of the initial product candidate from the FDA or the European Commission. The net profits and net losses, as applicable, incurred under the A&R Vertex JDCA with respect to all product candidates and products specified in the A&R Vertex JDCA other than exa-cel shall be shared equally between us and Vertex. With respect to exa-cel only, the net profits and net losses, as applicable, incurred under the A&R Vertex JDCA through July 1, 2021 in connection with the initial shared product (i.e., exa-cel) were shared equally between us and Vertex, and beginning July 1, 2021, the net profits and net losses, as applicable, incurred under the A&R Vertex JDCA are allocated 40% to CRISPR and 60% to Vertex. In addition, the A&R Vertex JDCA allows us to defer a portion of our share of costs under the arrangement if spending on the exa-cel program exceeds specified amounts. Any deferred amounts are only payable to Vertex as an offset against future profitability of the exa-cel program and the amounts payable are capped at a specified maximum amount per year.

Termination. Either party can terminate the A&R Vertex JDCA upon the other party's material breach, subject to specified notice and cure provisions, or, in the case of Vertex, in the event that we become subject to specified bankruptcy, winding up or similar circumstances. Either party may terminate the A&R Vertex JDCA in the event the other party commences or participates in any action or proceeding challenging the validity or enforceability of any patent that is licensed to such challenging party pursuant to the A&R Vertex JDCA. Vertex also has the right to terminate the A&R Vertex JDCA for convenience at any time after giving prior written notice.

If circumstances arise pursuant to which a party would have the right to terminate the A&R Vertex JDCA on account of an uncured material breach, such party may elect to keep the A&R Vertex JDCA in effect and cause such breaching party to be treated as if it had exercised its opt-out rights with respect to the products associated with such uncured material breach (described below) and the royalties payable to the breaching party would be reduced by a specified percentage.

Opt-Out Rights. Either party may opt out of the development of a product candidate under the A&R Vertex JDCA after predetermined points in the development of the product candidate, on a candidate-by-candidate basis. In the event of such opt-out, the party opting out will no longer share in the net profits and net losses associated with such product candidate and, instead, the opting-out party will be entitled to high single to mid-teen percentage royalties on the net sales of such product, if commercialized.

2019 Collaboration Agreement

In June 2019, we and Vertex entered the 2019 Collaboration Agreement, pursuant to which we and Vertex agreed to collaborate to develop and commercialize products for the treatment of DMD and DM1. We and Vertex amended the 2019 Collaboration Agreement in April 2021.

The 2019 Collaboration Agreement includes, among other things, provisions relating to the following:

Governance. We and Vertex will form a joint advisory committee to provide high-level oversight and coordination of the activities covered by the 2019 Collaboration Agreement.

Development and Commercialization. The 2019 Collaboration Agreement provides that Vertex will be responsible for development and commercialization activities, subject to our option, exercisable during a specified exercise period, to co-develop and co-commercialize products for the treatment of DM1.

Financial Terms. In connection with entering into the 2019 Collaboration Agreement, we received a $175.0 million up-front payment from Vertex. We are eligible to receive milestone payments from Vertex of up to $775.0 million in the aggregate, depending on the numbers and types of products that achieve pre-determined development and commercial milestones. We are also eligible to receive royalties on the sales of products ranging from the low single digits to the low double digits.

Co-Development and Co-Commercialization Option. If we elect to co-develop and co-commercialize products for the treatment of DM1, we would reimburse Vertex for fifty percent (50%) of the DM1 research and development costs incurred by Vertex and

would be responsible for fifty percent (50%) of such costs going forward. We would receive, in lieu of further milestone or royalty payments associated with DM1 development and commercialization activities, fifty percent (50%) of all profits from sales of such products and would be responsible for fifty percent (50%) of all losses.

Termination. Either party may terminate the 2019 Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. We may also terminate the 2019 Collaboration Agreement in the event Vertex commences or participates in any action or proceeding challenging the validity or enforceability of any patent that is licensed to Vertex pursuant to the 2019 Collaboration Agreement. Vertex may also terminate the 2019 Collaboration Agreement upon our bankruptcy or insolvency, or for convenience at any time, after giving written notice.

If circumstances arise pursuant to which Vertex would have the right to terminate the 2019 Collaboration Agreement on account of an uncured material breach, Vertex may elect to keep the 2019 Collaboration Agreement in effect and reduce by a specified percentage the applicable royalties payable in respect of the product(s) that are the subject of the breach.

Bayer

In December 2019, we and Bayer entered into an option agreement, or the 2019 Option Agreement, in connection with the termination of our joint venture with Bayer established to discover, develop and commercialize CRISPR/Cas9 gene editing therapeutics to treat the genetic causes of certain diseases. Under the 2019 Option Agreement, Bayer obtained an option (exercisable during a specified exercise period defined by future events, but in no event longer than five years after the effective date of the 2019 Option Agreement) to co-develop and co-commercialize two products for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders. In the event Bayer elects to co-develop and co-commercialize a product, the parties will negotiate and enter into a co-development and co-commercialization agreement, or a Co-Commercialization Agreement, for such product, and Bayer would be responsible for 50% of the research and development costs incurred by us for such product going forward. Bayer would receive 50% of all profits from sales of such product and would be responsible for 50% of all losses.

If Bayer elects to exercise its option to co-develop and co-commercialize a product, Bayer will make a one-time $20.0 million payment, or the Option Payment, to us that will become non-refundable once the parties execute a Co-Commercialization Agreement with respect to such optioned product. The Option Payment is payable only once with respect to the first time Bayer exercises an option under the 2019 Option Agreement.

In addition, following Bayer's exercise of its option and/or the execution of a co-commercialization agreement for an optioned product, for a period beginning on the effective date of such co-commercialization agreement and ending on the earlier of the three-month anniversary of such effective date or during the 90-day negotiation process of such co-commercialization agreement, Bayer has a right to negotiate an exclusive license to develop and commercialize such optioned product. If Bayer exercises such right, the parties will enter into an exclusive license agreement for such optioned product on terms mutually agreeable to the parties. Further, the Option Payment paid for such optioned product would become credited against payments due under such exclusive license or any other exclusive license entered into in connection with the 2019 Option Agreement.

Either party may terminate the 2019 Option Agreement upon the other party's material breach, subject to specified notice and cure provisions. We may also terminate the 2019 Option Agreement in the event Bayer commences or participates in any action or proceeding challenging the validity or enforceability of any CRISPR patent necessary or useful for the research, development, manufacture or commercialization of a product that is the subject of the 2019 Option Agreement. Bayer may also terminate the 2019 Option Agreement upon our bankruptcy or insolvency, or for convenience at any time, after giving written notice.

The foregoing descriptions of our strategic agreements are qualified in their entirety by reference to the full text of such agreements, copies of which are filed as exhibits to this Annual Report on Form 10-K.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions, know-how and improvements that we believe are commercially important to our business by seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties, that cover our gene editing technology, and existing and planned therapeutic programs. We also rely on trade secret protection and confidentiality agreements to protect our proprietary technologies and know-how to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, as well as continuing technological innovation and seeking in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene editing. We additionally rely on trademark protection, copyright protection and regulatory protection available via orphan drug designations, data exclusivity, market exclusivity, and, if relevant, patent term extensions. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for our technology, our ability to defend and enforce our intellectual property rights and our ability to operate without infringing any valid and enforceable patents and proprietary rights of third parties. We also

protect the integrity and confidentiality of our data, know-how and trade secrets by maintaining physical security of our premises and physical and electronic security of our information systems.

In-Licensed Intellectual Property from Dr. Charpentier

In April 2014, pursuant to an exclusive license with Dr. Charpentier, we licensed certain rights to a worldwide patent portfolio which covers various aspects of our gene editing platform technology including, for example, compositions of matter (e.g., CRISPR/Cas9 systems) and methods of use, including the use of CRISPR/Cas9 systems for gene editing. We refer to this worldwide patent portfolio as the "Patent Portfolio". This Patent Portfolio to-date includes, for example, more than ninety-five (95) granted or allowed patents in the United States, United Kingdom, Canada, Germany, Europe, Japan, China, India, Ukraine, New Zealand, Singapore, Australia, Mexico, Tunisia, Hong Kong, Israel, Peru, the Philippines, and South Africa and pending patent applications in the United States, Europe, Canada, Mexico, Australia and other selected countries in Central America, South America, Asia and Africa. This license is limited to therapeutic products such as pharmaceuticals and biologics and any associated companion diagnostics, for the treatment or prevention of human diseases, disorders, or conditions. For further information about this license, please see "*Business— License Agreements—CRISPR License with Dr. Charpentier*."

In addition to Dr. Charpentier, the Patent Portfolio has named inventors who assigned their rights either to the Regents of the University of California, or California, or the University of Vienna, or Vienna. California's rights are subject to certain overriding obligations to the sponsors of its research, including the Howard Hughes Medical Institute and the U.S. Government. Caribou Biosciences, or Caribou, had reported that it had an exclusive license to patent rights from California and Vienna, subject to a retained right to allow non-profit entities to use the inventions for research and educational purposes. Intellia Therapeutics, Inc., or Intellia Therapeutics, had reported that it had an exclusive license to such rights from Caribou in certain fields. We refer collectively to Dr. Charpentier, California, and Vienna as the "CVC Group". We are subject to quasi-litigation, inter partes administrative proceedings in the U.S. Patent and Trademark Office, or USPTO, and the European Patent Office involving the Patent Portfolio. For further information regarding risks regarding these proceedings, please see "*Risk Factors—Risks Related to Intellectual Property*."

On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement, or the IMA, with California, Vienna, Dr. Charpentier, Intellia Therapeutics, Caribou, ERS Genomics Ltd., or ERS, and our wholly-owned subsidiary TRACR Hematology Ltd., or TRACR. Under the IMA, California and Vienna retroactively consent to Dr. Charpentier's licensing of her rights to the CRISPR/Cas9 intellectual property, pursuant to our license with Dr. Charpentier, to us, TRACR, and ERS, in the United States and globally. The IMA also provides retroactive consent of co-owners to sublicenses granted by us, TRACR and other licensees, prospective consent to sublicenses they may grant in future, retroactive approval of prior assignments by certain parties, and provides for, among other things, (i) good faith cooperation among the parties regarding patent maintenance, defense and prosecution, (ii) cost-sharing arrangements, and (iii) notice of and coordination in the event of third-party infringement of the subject patents and with respect to certain adverse claimants of the CRISPR/Cas9 intellectual property. Unless earlier terminated by the parties, the IMA will continue in effect until the later of the last expiration date of the patents underlying the gene editing technology, or the date on which the last underlying patent application is abandoned. For further information regarding the effects of joint ownership in the United States and in other jurisdictions worldwide, please see "*Risk Factors—The Intellectual Property That Protects Our Core Gene Editing Technology Is Jointly Owned, And Our License Is From Only One Of The Joint Owners, Materially Limiting Our Rights In The United States And In Other Jurisdictions*."

CRISPR-Owned Intellectual Property

In addition to the Patent Portfolio, we have a broad intellectual property estate that includes numerous patent families covering key aspects of our CRISPR/Cas9 technologies and development programs which is intended to provide multiple layers of protection. These patent families encompass filings covering our development programs (such as composition of matter, method of use, manufacturing processes, dosing and formulations), the use and improvement modifications of CRISPR/Cas9 systems for gene editing (such as improvements to component systems including nucleases and single or modified guide RNAs), technologies for delivering protein/nucleic acid complexes and RNA into cells (such as improved viral vector systems and self-inactivating systems), and technology relevant to stem cell-based therapies.

Overall, our intellectual property estate includes over one hundred (100) active patent families and over forty (40) granted or allowed patents in the United States, China, Europe, and South Africa, and pending patent applications in the United States, Europe, Australia, Canada, China, Japan, Mexico and other selected countries in Central America, South America, the Middle East, Asia and Africa. The granted patents and any other patents that may ultimately issue from these patent families are expected to expire starting in 2033, not including any applicable patent term extensions.

Our U.S. trademark estate consists of over twenty (20) pending applications, including for example, for COBALT, CRISPRX, CRISPR THERAPEUTICS, CRISPR TX, CTX001, CTX130, VCTX210, and VCTX211, as well as seven U.S. registrations, including for CRISPR THERAPEUTICS, the CRISPR THERAPEUTICS logo, and CTX110. Our international trademark estate consists of multiple pending applications and registrations, including a pending application for CRISPR THERAPEUTICS in Germany and four registrations in UK, Italy, Spain and Benelux, and twelve (12) registrations for CRISPR THERAPEUTICS & DESIGN in Brazil, Benelux, Germany, Hong Kong, Italy, South Africa and Spain and three pending applications for COBALT in

Hong Kong and South Africa. We also have six International Registrations, including for CTX112 designating the EU, Switzerland, and UK, CTX131 designating the EU, Switzerland, and UK, and CRISPR THERAPEUTICS logo designating Canada, Switzerland, Japan, Korea, Mexico, Russia, Singapore, and UK.

Patent Assignment Agreement

In November 2014, we entered into a patent assignment agreement with Dr. Charpentier, Dr. Ines Fonfara and Vienna, or the Patent Assignment Agreement. Under the Patent Assignment Agreement, Dr. Charpentier, Dr. Fonfara and Vienna assigned to us all rights to a family of patent applications relating to certain compositions of matter, including additional CRISPR/TRACR/Cas9 complexes, and methods of use, including their use in targeting or cutting DNA.

As consideration for the patent rights assigned to us, we agreed to pay an upfront payment, milestone payments beginning with the filing of a U.S. Investigational New Drug application or its equivalent in another country, a minimum annual royalty, a low single-digit royalty on net sales of products whose manufacture, use, sale, or importation is covered by the assigned patent rights, and a low single-digit percentage of licensing revenues.

We are obligated to use commercially reasonable efforts to obtain regulatory approval to market a product whose manufacture, use, sale, or importation is covered by the assigned patent rights, including but not limited to an obligation to use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) by November 2021.

License Agreements

CRISPR License With Dr. Charpentier

In April 2014, we entered into a license agreement, or the Charpentier License Agreement, with Dr. Charpentier, one of our co-founders, pursuant to which we received an exclusive license under Dr. Charpentier's joint ownership interest in the Patent Portfolio, to research, develop and commercialize therapeutic products such as pharmaceuticals or biological preparations, and any associated companion diagnostics, for the treatment or prevention of human diseases, disorders, or conditions, other than hemoglobinopathies, which we refer to as the CRISPR Field. The license is exclusive, even as to Dr. Charpentier, except that she retains a non-transferable right to use the technology for her own research purposes and in research collaborations with academic and non-profit partners. The exclusive license is granted only under Dr. Charpentier's interest in the patent applications and the exclusivity is not granted under any other joint owner's interest. Additionally, the Charpentier License Agreement granted us an exclusive, worldwide, royalty-free sublicense, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic products relating to the CRISPR Field which incorporate any intellectual property that TRACR develops under its license with Dr. Charpentier. In turn, we granted to Dr. Charpentier an exclusive license with the obligation to sublicense to TRACR any intellectual property we develop under the license with Dr. Charpentier for treatment and prevention of hemoglobinopathies in humans, including, without limitation, sickle cell disease and thalassemia.

Under the terms of the Charpentier License Agreement, as consideration for the license, Dr. Charpentier received a technology transfer fee, an immaterial annual maintenance fee, immaterial milestone payments that will be due after the initiation of clinical trials, a low single digit percentage royalty on net sales of licensed products, and a low single digit percentage royalties of sublicensing revenue. We are obligated to use commercially reasonable efforts to obtain regulatory approval to market a licensed therapeutic product. We must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country for a therapeutic product in the CRISPR field) by April 2021. In addition, we must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the CRISPR field by April 2024.

Unless terminated earlier, the term of the Charpentier License Agreement will expire on a country-by-country basis, upon the expiration of the last to expire valid claim of the Patent Portfolio in such country. We have the right to terminate the agreement at will upon 60 days' written notice to Dr. Charpentier. We and Dr. Charpentier may terminate the agreement upon 90 days' notice in the event of a material breach by the other party, which is not cured during the 90-day notice period. Dr. Charpentier may terminate the license agreement immediately if we challenge the enforceability, validity, or scope of any Patent Portfolio.

TRACR License With Dr. Charpentier

In April 2014, concurrently with our license agreement with Dr. Charpentier, TRACR entered into a license agreement, or the TRACR License Agreement, with Dr. Charpentier, a minority shareholder of TRACR, under the Patent Portfolio. Pursuant to the TRACR License Agreement, TRACR was granted an exclusive, worldwide, royalty-bearing license, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic and diagnostic products for the treatment and prevention of hemoglobinopathies in humans, including sickle cell disease and thalassemia, or the TRACR Field. TRACR also received a non-exclusive, worldwide, royalty-free license, including the right to sublicense, to carry out internal pharmaceutical research for

therapeutic products outside of the TRACR Field and an exclusive, worldwide, royalty-free sublicense, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic products relating to the TRACR Field which incorporate any intellectual property that CRISPR develops under its license with Dr. Charpentier. In turn, TRACR granted to Dr. Charpentier an exclusive license to sublicense to CRISPR any intellectual property that TRACR develops under the license with Dr. Charpentier for use in the CRISPR Field.

TRACR is obligated to use commercially reasonable efforts to research, develop, and commercialize at least one therapeutic product for the prevention or treatment of human disease under the license agreement. TRACR must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the TRACR field by April 2021. In addition, TRACR must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the TRACR field by April 2024. TRACR is solely responsible for all clinical, regulatory and development costs.

Under the TRACR License Agreement, Dr. Charpentier is entitled to receive immaterial clinical and regulatory milestone payments per product that TRACR commercializes. TRACR is also required to pay Dr. Charpentier low single digit percentage royalties on the net sales of any approved therapeutic or diagnostic products, made by it, its affiliates, or its sublicensees and low single-digit percentage royalties on sublicensing revenue.

Unless terminated earlier, the term of the license agreement will expire on a country-by-country basis, upon the expiration of the last to expire valid claim of the Patent Portfolio in such country. TRACR has the right to terminate the agreement at will upon 60 days' written notice to Dr. Charpentier. TRACR and Dr. Charpentier may terminate the agreement upon 90 days' notice in the event of a material breach by the other party, which is not cured during the 90-day notice period. Dr. Charpentier may terminate the license agreement immediately if TRACR challenges the enforceability, validity, or scope of any Patent Right.

Enabling Technologies

We have entered into a number of additional collaborations and license agreements to support and complement our *ex vivo* and *in vivo* programs, including agreements related to: technologies to deliver CRISPR/Cas9 *ex vivo* and *in vivo*; additions to our hematopoietic stem cell and *in vivo* programs, including a grant to advance gene editing therapies for HIV; and enhancements to our immuno-oncology and regenerative medicine cell therapy programs and platform. For example, we have entered into agreements with Nkarta, Inc. to co-develop and co-commercialize two donor-derived, gene-edited CAR-NK cell product candidates and a product candidate combining NK and T cells; Capsida Biotherapeutics, Inc. to develop *in vivo* gene editing therapies delivered with engineered AAV vectors for the treatment of amyotrophic lateral sclerosis and Friedreich's ataxia; Moffitt Cancer Center and Roswell Park Comprehensive Cancer Center to advance autologous CAR T programs against new targets; MaxCyte Incorporated on *ex vivo* delivery for our hemoglobinopathy and immuno-oncology programs; CureVac AG on optimized mRNA constructs and manufacturing for certain *in vivo* programs; and KSQ Therapeutics Incorporated on intellectual property for our allogeneic immuno-oncology programs.

Manufacturing

The manufacturing processes for cell and genetic therapies are complex and require customized systems, equipment, facilities and expertise for each program and therapy. In the second quarter of 2020, we announced an investment to construct our own cell therapy manufacturing facility in Framingham, Massachusetts for clinical and commercial production of our product candidates and certain components thereof for certain of our programs. In the fourth quarter of 2021, we completed construction of this facility, and currently we are progressing the regulatory validation activities required to bring this facility into compliance with current Good Manufacturing Practice, or cGMP, and to enable us to produce cell therapy product supply suitable for human administration in the future. The facility comprises approximately 50,249 square feet.

We will continue to rely on external manufacturing capabilities realized via contract manufacturing organization relationships in the United States and abroad. We have entered into certain manufacturing and supply arrangements with third-party suppliers to support production of our product candidates and their components. We plan to continue to rely on qualified third-party organizations to produce or process bulk compounds, formulated compounds, viral vectors or engineered cells for IND-supporting activities and early stage clinical trials. We expect that commercial quantities of any compound, vector, or engineered cells that we may seek to develop will be manufactured in facilities and by processes that comply with FDA and other regulations. At the appropriate time in the product development process, we will determine whether to utilize our own manufacturing facility or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop.

We continue to expect to make significant investment in our manufacturing capabilities in Framingham, Massachusetts and in partnerships with third-party organizations for our gene editing programs in order to continue to advance and, in the future, commercialize these programs.

In addition, as product candidates advance through our pipeline, our commercial plans may change. In particular, some of our research programs target potentially larger indications. Data, the size of the development programs, the size of the target market, the size of a commercial infrastructure and manufacturing needs may all influence our strategies in the United States, Europe and the rest of the world. Outside of the United States and Europe, where appropriate, we may elect in the future to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

Competition

The biotechnology and pharmaceutical industries, including in the gene editing, gene therapy and cell therapy fields, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property and proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we currently face, and will continue to face, substantial competition from many different sources, including large pharmaceutical, specialty pharmaceutical and biotechnology companies; academic institutions and governmental agencies; and public and private research institutions, some or all of which may have greater access to capital or resources than we do. For any products that we may ultimately commercialize, not only will we compete with any existing therapies and those therapies currently in development, but we will also have to compete with new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that utilize technologies encompassing genomic medicines to create therapies, including gene editing, gene therapy and cell therapy. In addition, we compete with companies working to develop therapies in areas related to our specific research and development programs.

Our platform and product focus is on the development of therapies using CRISPR/Cas9 gene editing technology. We are aware of several companies focused on developing therapies in various indications using CRISPR/Cas9 gene editing technology, including Intellia Therapeutics and Editas Medicine. In addition, several academic groups have developed new gene editing technologies based on CRISPR/Cas9, such as base editing and prime editing, that may have utility in therapeutic development. Companies seeking to develop therapies based on these technologies include Beam Therapeutics and Prime Medicine.

There are also companies developing therapies using additional gene editing technologies, such as TALENs, meganucleases and ZFNs. These companies include 2seventy bio, Allogene Therapeutics, Cellectis, Precision BioSciences and Sangamo Therapeutics.

We are also aware of companies developing therapies in various areas related to our specific research and development programs. In hemoglobinopathies, these companies include Beam Therapeutics, bluebird bio, Editas Medicine, Graphite Bio, Merck, Novartis Pharmaceuticals, Pfizer, and Sangamo Therapeutics. In immuno-oncology, these companies include 2seventy bio, Adicet Bio, Allogene Therapeutics, Bristol Myers Squibb, Caribou Biosciences, Cellectis, Century Therapeutics, Fate Therapeutics, Gilead Sciences, Legend Biotech, Novartis Pharmaceuticals, Poseida Therapeutics and Precision BioSciences. In regenerative medicine, these companies include BlueRock Therapeutics (acquired by Bayer in 2019), Sana Biotechnology and Semma Therapeutics (acquired by Vertex in 2019). In *in vivo*, these companies include Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, BioMarin Pharmaceutical, Intellia Therapeutics, Ionis Pharmaceuticals, Regeneron Pharmaceuticals and Verve Therapeutics. Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications and there can be no certainty that other gene editing technologies will not be considered better or more attractive than our technology for the development of products. For example, Cas9 may be determined to be less attractive than other CRISPR proteins, such as Cas12a or novel Cas enzymes that have yet to be discovered, or other CRISPR-associated nuclease variants that can edit human DNA, such as base editors and prime editors.

Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications and there can be no certainty that other gene editing technologies will not be considered better or more attractive than our technology for the development of products. For example, Cas9 may be determined to be less attractive than other CRISPR proteins, such as Cas12a or novel Cas enzymes that have yet to be discovered, or other CRISPR-associated nuclease variants that can edit human DNA, such as base editors and prime editors.

In addition to competition from other gene editing therapies or gene or cell therapies, any product we may develop may also face competition from other types of therapies, such as small molecule, antibody or protein therapies. In addition, new scientific discoveries may cause CRISPR/Cas9 technology, or gene editing as a whole, to be considered an inferior form of therapy.

In addition, many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene and cell 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. 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, have broader acceptance and higher rates of reimbursement by third-party payors or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, convenience, and availability of reimbursement.

If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene editing, gene therapy, and cell therapy products. Competition with other related products currently under development may include competition for clinical trial sites, patient recruitment, and product sales. In addition, due to the intense research and development taking place in the gene editing field, including by us and our competitors, the intellectual property landscape is in flux and highly competitive. There may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third-party, intellectual property and proprietary rights in the future. For example, see our discussion of the ‘048 interference, the ‘115 interference and European opposition proceedings in "*Risk Factors—Risks Related to Intellectual Property—Third-party Claims Of Intellectual Property Infringement Against Us, Our Licensors Or Our Collaborators May Prevent Or Delay Our Product Discovery and Development Efforts.*"

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products, including biological products. Some jurisdictions outside of the United States also regulate the pricing of such products. The processes for obtaining marketing approvals in the United States and in other countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Licensure and Regulation of Biologics in the United States

In the United States, our product candidates are regulated as biological products, or biologics, under the Public Health Service Act, or PHSA, and the Federal Food, Drug, and Cosmetic Act, or FDCA, and their implementing regulations. The failure to comply with the applicable U.S. requirements at any time during the product development process, including nonclinical testing, clinical testing, the approval process or post-approval process, may subject an applicant to delays in the conduct of a study, regulatory review and approval, and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA’s refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, untitled or warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, and civil or criminal investigations and penalties brought by the FDA or the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new biologic in the United States generally must satisfactorily complete each of the following steps:

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA’s Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an Investigational New Drug, or IND, application for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated, or by a central IRB if appropriate;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency, and purity of the product candidate for each proposed indication, in accordance with the FDA’s Good Clinical Practice, or GCP, regulations;

- preparation and submission to the FDA of a Biologics License Application, or BLA, for a biologic product requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product and proposed labeling;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, 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, and, if applicable, the FDA's current good tissue practice, or CGTP, for the use of human cellular and tissue products;
- satisfactory completion of any FDA audits of the nonclinical study and clinical trial sites to assure compliance with GLPs and GCPs, respectively, and the integrity of clinical data in support of the BLA;
- payment of user fees and securing FDA approval of the BLA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, adverse event reporting, and compliance with any post-approval studies required by the FDA.

Preclinical Studies and Investigational New Drug Application

Before testing any biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate the potential for efficacy and toxicity in animals. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA imposes a clinical hold based on concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects would be exposed to unreasonable and significant health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin.

As a result, submission of the IND may result in the FDA not allowing the trials to commence or not allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the conduct of the IND study, including safety concerns or concerns due to non-compliance, it may impose a partial or complete clinical hold. This order issued by the FDA would either delay a proposed clinical study or cause suspension of an ongoing study, or in the case of a partial clinical hold limit a study, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed or recommence but only under terms authorized by the FDA. This could cause significant delays or difficulties in completing planned clinical studies in a timely manner.

Human Clinical Trials in Support of a BLA

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under study protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a non-U.S. clinical trial is not conducted under an IND, the sponsor may submit data from a well-designed and well-conducted clinical trial to the FDA in support of the BLA so long as the clinical trial is conducted in compliance with GCP and the FDA is able to validate the data from the study through an onsite inspection if the FDA deems it necessary.

Further, each clinical trial must be reviewed and approved by an IRB either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, subject informed consent, ethical factors, and the safety of human subjects. An IRB must operate in compliance with FDA regulations. The FDA or the clinical trial sponsor may suspend or terminate a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Additionally, some clinical trials are overseen by an

independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group may recommend continuation of the study as planned, changes in study conduct, or cessation of the study at designated check points based on access to certain data from the study.

In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules are subject to oversight of institutional biosafety committees, or IBCs, as set forth in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Under the NIH Guidelines, recombinant and synthetic nucleic acids are defined as: (i) molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell (i.e., recombinant nucleic acids); (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (i.e., synthetic nucleic acids); or (iii) molecules that result from the replication of those described in (i) or (ii). Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may be required after approval.

- ***Phase 1*** clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion, and pharmacodynamics in healthy humans or, on occasion, in patients, such as cancer patients.
- ***Phase 2*** clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and costlier Phase 3 clinical trials.
- ***Phase 3*** clinical trials are undertaken within an expanded patient population to further evaluate dosage and gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.

Progress reports detailing the results, if known, of the clinical trials must be submitted at least annually to the FDA. Written IND safety reports must be submitted to the FDA and the investigators within 15 calendar days of receipt by the sponsor or its agents after determining that the information qualifies for such expedited reporting. IND safety reports are required for serious and unexpected suspected adverse events, findings from other studies or animal or *in vitro* testing that suggest a significant risk to humans exposed to the drug, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Additionally, a sponsor must notify FDA within 7 calendar days after receiving information concerning any unexpected fatal or life-threatening suspected adverse reaction.

In some cases, the FDA may approve a BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Guidance Governing Gene Therapy Products

The FDA has defined a gene therapy product as one that mediates its effects by transcription and/or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site specific nucleases used for human genome editing and *ex vivo* genetically modified human cells. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient. Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. Within the CBER, the review of gene therapy and related products is consolidated in the Office of Therapeutic Products, and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols.

Although the FDA has indicated that its guidance documents regarding gene therapies are not legally binding, we believe that our compliance with them is likely necessary to gain approval for any product candidate we may develop. The guidance documents provide additional factors that the FDA will consider at each of the above stages of development and relate to, among other things, the

proper preclinical assessment of gene therapies; the chemistry, manufacturing, and control information that should be included in an IND application; the 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 who have been exposed to investigational gene therapies when the risk of such effects is high. Further, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events. Depending on the product type, long term follow up can be up to 15 years or as little as five years.

Compliance with cGMP and CGTP Requirements

Before approving a BLA, the FDA typically will inspect 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 are in full compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined.

For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with CGTP. These requirements are found in FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission, and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing.

Manufacturers and others involved in the manufacture and distribution of products, and those supplying products, ingredients, and components of them, must also register their establishments with the FDA and certain state agencies for products intended for the U.S. market, and with analogous health regulatory agencies for products intended for other markets globally. Both U.S. and non-U.S. manufacturing establishments must register and provide additional information to the FDA and/or other health regulatory agencies upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether U.S. or non-U.S., is deemed misbranded under the FDCA, and could be affected by similar as well as additional compliance issues in other jurisdictions. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA or other governing health regulatory agency may lead to a product being deemed to be adulterated.

Review and Approval of a BLA

The results of product candidate development, preclinical testing, and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a BLA requesting a license to market the product. The BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether it is sufficient to accept for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or the PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs. The review process may often be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by three months if the FDA requests or if the applicant otherwise provides through the submission of a major amendment additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure, and potent and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure, and potent.

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of nonclinical study and clinical trial sites to assure compliance with GLPs and GCPs, respectively, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the application is not approved, the FDA will issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by an applicant in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission. The FDA will

not approve an application until issues identified in the complete response letter have been addressed. Alternatively, sponsors that receive a complete response letter may either withdraw the application or request a hearing.

The FDA may also refer the application to an advisory committee for review, evaluation, and recommendation as to whether the application should be approved. In particular, the FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates, and provides 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.

If the FDA approves a new product, it may limit the approved indications for use of the product. It may also require that contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, specific or special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, certain manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Expedited Programs

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review, and regenerative medicine advanced therapy designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process, or if the designated drug development program is no longer being pursued.

Second, FDA has a regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either 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. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting adverse reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Finally, the FDA can accelerate review and approval of products designated as regenerative medicine advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative medicine advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

In addition, under the Food and Drug Omnibus Reform Act of 2022 ("FDORA"), a platform technology incorporated within or utilized by a drug or biological product is eligible for designation as a designated platform technology if (1) the platform technology is incorporated in, or utilized by, a drug approved under a BLA; (2) preliminary evidence submitted by the sponsor of the approved or licensed drug, or a sponsor that has been granted a right of reference to data submitted in the application for such drug, demonstrates that the platform technology has the potential to be incorporated in, or utilized by, more than one drug without an adverse effect on quality, manufacturing, or safety; and (3) data or information submitted by the applicable person indicates that incorporation or utilization of the platform technology has a reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process. A sponsor may request the FDA to designate a platform technology as a designated platform technology concurrently with, or at any time after, submission of an IND application for a drug that incorporates or utilizes the platform technology that is the subject of the request. If so designated, the FDA may expedite the development and review of any subsequent original BLA for a drug that uses or incorporates the platform technology. Designated platform technology status does not ensure that a drug will be developed more quickly or receive FDA approval. In addition, the FDA may revoke a designation if the FDA determines that a designated platform technology no longer meets the criteria for such designation.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally could support accelerated approval where a study demonstrates a relatively short-term clinical benefit in a chronic disease setting in which assessing durability of the clinical benefit is essential for traditional approval, but the short-term benefit is considered reasonably likely to predict long-term benefit.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit, and the FDA is now permitted to require, as appropriate, that such trials be underway prior to approval or within a specific time period after the date of approval for a product granted accelerated approval. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA has imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers are required to comply with applicable product tracking and tracing requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money, and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that 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 lot release, the manufacturer must submit

samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency, and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences of a failure to comply with regulatory requirements include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, untitled or warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of licensed and approved products that are placed on the market. Pharmaceutical products may be promoted 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.

Orphan Drug Designation

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the United States or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the biologic for the disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation qualifies a company for tax credits and market exclusivity for seven years following the date of the product's marketing approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan when it receives orphan drug designation from the Office of Orphan Products Development, or OOPD, at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process for commercial distribution like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first drug. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. The FDA cannot, however, approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003 (PREA), as amended, a BLA or supplement thereto 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. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information

required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation; however, they will apply to a BLA for a new active ingredient that is orphan-designated if the biologic is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, or ACA, which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

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." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that 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.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity, and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products, and FDA may approve multiple "first" interchangeable products so long as they are all approved on the same first day of marketing. This exclusivity period, which may be shared amongst multiple first interchangeable products, lasts until the earlier of: (1) one year after the first commercial marketing of the first interchangeable product; (2) 18 months after resolution of a patent infringement suit instituted under 42 U.S.C. § 262(l)(6) against the applicant that submitted the application for the first interchangeable product, based on a final court decision regarding all of the patents in the litigation or dismissal of the litigation with or without prejudice; (3) 42 months after approval of the first interchangeable product, if a patent infringement suit instituted under 42 U.S.C. § 262(l)(6) against the applicant that submitted the application for the first interchangeable product is still ongoing; or (4) 18 months after approval of the first interchangeable product if the applicant that submitted the application for the first interchangeable product has not been sued under 42 U.S.C. § 262(l)(6). At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

Patent Term Restoration and Extension

A patent claiming a new biologic product may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of an IND and the submission date of a marketing application, plus the time between the submission date of the marketing application and the ultimate approval date, less any time the applicant failed to act with due diligence. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Regulation And Procedures Governing Approval Of Medicinal Products In Europe

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable health regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in Europe generally follows the same lines as in the United States, although the approval of a medicinal product in the United States is no guarantee of approval of the same product in Europe, either at all or within the same timescale as approval may be granted in the United States. The process entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the EMA, or the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by the EMA or these authorities before the product can be marketed and sold in Europe.

Clinical Trial Approval

An applicant for a clinical trial authorization in the EU must obtain approval from the national competent authority, or NCA, of an EU Member State in which the clinical trial is to be conducted, or in multiple Member States if the clinical trial is to be conducted in a number of Member States. Furthermore, the applicant may only start a clinical trial at a specific study site after the ethics committee, or EC, has issued a favorable opinion in relation to the clinical trial.

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which replace the Clinical Trials Directive 2001/20/EC on 31 January 2022. It overhauls the current system of approvals for clinical trials in the EU. Specifically, the new legislation, which is directly applicable in all EU Member States (meaning that no national implementing legislation in each EU Member State is required), aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single-entry point and strictly defined deadlines for the assessment of clinical trial applications.

Marketing Authorization

To obtain a marketing authorization for a product in the EU, an applicant must submit an MAA, either under a centralized procedure administered by the EU or one of the procedures administered by competent authorities in the EU Member States (decentralized procedure, national procedure, or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the EEA (comprising the EU Member States plus Iceland, Norway and Liechtenstein). Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EEA, an applicant must demonstrate compliance with all measures included in an EMA-approved pediatric investigation plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid throughout the EEA. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, or ATMPs, and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer, HIV or AIDS, diabetes, neurodegenerative disorders, auto-immune and other immune dysfunctions and viral diseases. For those products for which the use of the centralized procedure is not mandatory, applicants may elect to use the centralized procedure where either the product contains a new active substance indicated for the treatment of other diseases, or where the applicant can show that the product constitutes a significant therapeutic, scientific or technical innovation or for which a centralized process is in the interest of patients at an EU level.

Specifically, the grant of marketing authorization in the EU for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation (EC) No 1394/2007 on ATMPs, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation (EC) No 1394/2007 lays down specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to the Committee for Advanced Therapies, or CAT, at the EMA, which conducts a scientific assessment of the MAA and provides an opinion regarding the MAA for an ATMP. The European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

The Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for issuing a final opinion on whether an ATMP meets the required quality, safety and efficacy requirements, and whether a product has a positive benefit/risk profile. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days from receipt of a valid MAA, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Clock stops may extend the timeframe of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, it provides the opinion, together with supporting

documentation, to the European Commission, who make the final decision to grant a marketing authorization, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time frame of 210 days for assessment will be reduced to 150 days (excluding clock stops), but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment.

Now that the UK (which comprises Great Britain and Northern Ireland) has left the EU, Great Britain will no longer be covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland). All medicinal products with a current centralized marketing authorization were automatically converted to Great Britain marketing authorizations on January, 1 2021. For a period of three years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required.

PRIME scheme

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist, by, amongst other things, offering early dialogue with, and regulatory support from, the EMA. The scheme is intended to stimulate innovation, optimize development and enable accelerated assessment of PRIority Medicines, or PRIME, by building upon the scientific advice scheme and accelerated assessment procedure offered by EMA. The scheme is voluntary and eligibility criteria must be met for a medicine to qualify for PRIME.

The PRIME scheme is open to medicines under development and for which the applicant intends to apply for an initial marketing authorization application through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (meaning there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods or therapy or improving existing ones. Applicants will typically be at the exploratory clinical trial phase of development, and will have preliminary clinical evidence in patients to demonstrate the promising activity of the medicine and its potential to address, to a significant extent, an unmet medical need. In exceptional cases, applicants from the academic sector or SMEs (small and medium sized enterprises) may submit an eligibility request at an earlier stage of development if compelling non-clinical data in a relevant model provide early evidence of promising activity, and first in man studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.

If a medicine is selected for the PRIME scheme, the EMA:

- appoints a rapporteur from the CHMP or from the CAT to provide continuous support and to build up knowledge of the medicine in advance of the filing of a marketing authorization application;
- issues guidance on the applicant’s overall development plan and regulatory strategy;
- organizes a kick-off meeting with the rapporteur and experts from relevant EMA committees and working groups;
- provides a dedicated EMA contact person; and
- provides scientific advice at key development milestones, involving additional stakeholders, such as health technology assessment bodies and patients, as needed.

Medicines that are selected for the PRIME scheme are also expected to benefit from the EMA’s accelerated assessment procedure at the time of application for marketing authorization. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

Data and Market Exclusivity

In the EU, innovate medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon grant of a marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents applicants for authorizations of generics or biosimilars from referencing the innovator’s preclinical and clinical data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the EU, during a period of eight years from the date on which the reference product was first authorized in the EU. During the additional two-year period of market exclusivity, a generic or biosimilar MAA can be submitted and the innovator’s data may be referenced, but no generic or biosimilar medicinal product can be marketed in the EU until the expiration of the market exclusivity period. 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 authorization, are held to bring a significant clinical benefit in comparison with existing therapies. There is no guarantee that a product will be considered by the EMA to be an innovative medicinal

product, and products may qualify for data exclusivity. Even if a product is considered to be an innovative medicinal product so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained a marketing authorization based on an MAA with a completely independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

A centralized marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing EU Member State for a nationally authorized product. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization that is not followed by the actual placement of the drug on the EU market (in the case of the centralized procedure), or on the market of the authorizing EU Member State, within three years after authorization ceases, to be valid (the so-called sunset clause).

Orphan Drug Designation and Exclusivity

Regulation (EC) No 141/2000 and Regulation (EC) No 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish that: (1) the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five (5) in ten thousand (10,000) persons in the EU when the application is made; or (b) it is unlikely that the product, without benefits derived from orphan status, would generate sufficient return in the EU to justify the necessary investment in its development; (3) there exists no satisfactory method of diagnosis, prevention, or treatment of such condition authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the ability to apply for a centralized EEA-wide marketing authorization. The grant of a marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the European Commission nor the Member States can accept an application or grant a marketing authorization in respect of a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity. There are a few limited of derogations from the ten-year period of market exclusivity pursuant to which the European Commission may grant a marketing authorization for a similar medicinal product in the same therapeutic indication, which are:

- where the second applicant can establish that although their product is similar to the orphan medicinal product already authorized, the second product is safer, more effective or otherwise clinically superior;
- where the marketing authorization holder consent to the second orphan medicinal product application; or
- where the marketing authorization holder cannot supply enough orphan medicinal product.

Regulatory Requirements after Marketing Authorization has been obtained

If an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include compliance with the EU's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU. Finally, the marketing and promotion of authorized products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU. The advertising of prescription-only medicines to the general public is not permitted in the EU.

The aforementioned EU rules are generally applicable in the EEA, which consists of the EU Member States, plus Norway, Liechtenstein and Iceland.

For other markets in which we might in the future seek to obtain marketing approval for the commercialization of products, there are other health regulatory regimes for seeking approval, and we would need to ensure ongoing compliance with applicable health regulatory procedures and standards, as well as other governing laws and regulations for each applicable jurisdiction.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, ensuring certain accountability measures are in place and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the UK voted in favor of leaving the EU (commonly referred to as "Brexit"), and the UK formally left the EU on January 31, 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on December 31, 2020. However, the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore aligns in many ways with EU regulations, however it is possible that these regimes will more significantly diverge in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation.

Furthermore, the EU's GDPR (subject to small amendments) was incorporated into UK law by virtue of section 3 of the European Union (Withdrawal) Act of 2018 and the Data Protection Act of 2018 in the United Kingdom "implements" and complements the EU's GDPR. On June 28, 2021, the European Commission adopted an adequacy decision in respect of transfers of personal data to the United Kingdom for a four-year period (until 27 June 2025). Similarly, the United Kingdom has determined that it considers all of the EU and EEA Member States to be adequate for the purposes of data protection. This ensures data flows between the United Kingdom and the EU and EEA remain unaffected.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such product candidates. Even if any product candidates we may develop are approved, sales of such product candidates will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers, and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such product candidates. Factors a payor considers in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and

services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover any product candidates we may develop could reduce physician utilization of such product candidates once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of various federal, state and/or local governments, as well as other payors, within the United States and in other countries globally, and the prices of pharmaceuticals have been a focus in these efforts. Governments and other payors have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for any product candidates we may develop will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of any product candidates we may develop to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies (so called health technology assessments, or HTAs) in order to obtain reimbursement or pricing approval. For example, the EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the level of discounting required in relation to the pricing of pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense.

As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU Member States, and parallel trade (arbitrage between low-priced and high-priced Member States), can further reduce prices. Special pricing and reimbursement rules may apply to orphan drugs. Inclusion of orphan drugs in reimbursement systems tend to focus on the medical usefulness, need, quality and economic benefits to patients and the healthcare system as for any drug. Acceptance of any medicinal product for reimbursement may come with cost, use and often volume restrictions, which again can vary by country. In addition, results-based rules of reimbursement may apply. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind, in exchange for or intended to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil U.S. False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious, or fraudulent or knowingly making, using, or causing to be made or used a false record or statement to avoid, decrease, or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the U.S. False Claims Act;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, collectively HIPAA, which imposes criminal and civil liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program (including private payors) or 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, any healthcare benefit program, regardless of the payor (e.g., public or private) 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;
- HIPAA, which impose obligations with respect to safeguarding the privacy, security, and transmission of individually identifiable information that constitutes protected health information, including mandatory contractual terms and restrictions on the use and/or disclosure of such information without proper authorization;
- the federal transparency requirements known as the federal U.S. Physician Payments Sunshine Act, under the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, or HHS, information related to payments and other transfers of value made by that entity to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician providers such as physician assistants and nurse practitioners, and teaching hospitals, and requires certain manufacturers and applicable group purchasing organizations to report ownership and investment interests held by physicians or their immediate family members;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- The Foreign Corrupt Practices Act prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and
- analogous laws and regulations in other national jurisdictions and states, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state and other laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring pharmaceutical manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and other laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. For example, in California, the California Consumer Protection Act, or CCPA, which went into effect on January 1, 2020, establishes a new privacy

framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. While clinical trial data and information governed by HIPAA are currently exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope. In addition, a new California ballot initiative, the California Privacy Rights Act, or CPRA, was passed in November 2020. Effective starting on January 1, 2023, the CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. Further data privacy and security laws and regulations in foreign jurisdictions that may be more stringent than those in the United States (such as the European Union, which adopted the GDPR, which became effective in May 2018). Analogous state laws may additionally govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 70% point-of-sale-discount off the negotiated price of applicable products to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient products to be covered under Medicare Part D, increased pursuant to the Bipartisan Budget Act of 2018 which became effective as of 2019;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription product spending.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2031, in addition to a 4% pay-as-you-go or PAYGO sequester. Following a temporary suspension from May 1, 2020 through March 31, 2022 due to the coronavirus pandemic, a 1% payment reduction began April 1, 2022 through June 30, 2022, and the 2% payment reduction resumed on July 1, 2022. In addition, the Statutory Pay-As-You-Go Act of 2010, or PAYGO, requires that automatic payment cuts of 4% be applied to Medicare and affects certain providers. These cuts were slated to go into effect January 1, 2023, but the Consolidated Appropriations

Act, 2023, further delayed these cuts until 2025. Further, 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 providers, including hospitals, imaging centers, and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business.

At the federal level, President Biden signed an Executive Order on July 9, 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. On September 25, 2020, CMS stated drugs imported by states under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for "best price" or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a National Average Drug Acquisition Cost for these drugs. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates.

Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also created a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. This deadline was further pushed back to January 1, 2027 by the Bipartisan Safer Communities Act and later to January 1, 2032 by the Inflation Reduction Act of 2022 ("IRA").

Further, CMS finalized regulations that give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. It is unclear what type of impact, if any, efforts such as this will have on our business.

There has also been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in enacting legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Beyond challenges to the ACA, other legislative measures have also been enacted that may impose additional pricing and product development pressures on our business. For example, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is

no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy. We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

The IRA was signed into law in August 2022. The IRA includes several provisions that will impact our business to varying degrees, including provisions that allow the U.S. government to negotiate and set price caps for Medicare Part B and Part D pricing for certain high-cost, single-source drugs and biologics without generic or biosimilar competition; reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025, effectively eliminating the so-called "donut hole" for Medicare Part D; require companies to pay rebates to Medicare for drug prices that increase faster than inflation; and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge, among other areas. The effect of the IRA on our business and the healthcare industry in general is not yet known.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

There have been, and likely will continue to be, legislative and regulatory proposals at the national level in the United States and other jurisdictions globally, as well as at some regional, state and/or local levels within the United States or other jurisdictions, directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

Additional Regulation

In addition to the foregoing, state, and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act, and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling, and disposal of various biologic, chemical, and radioactive substances used in, and wastes generated by, operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. Equivalent laws have been adopted in third countries that impose similar obligations.

Human Capital

As of December 31, 2022, we had 458 full-time employees. No employees were represented by labor unions or subject to collective bargaining agreements. The majority of employees were based in Boston, Massachusetts with additional employees based in Framingham, Massachusetts, Mission Bay, California, Switzerland and the United Kingdom. 97 employees held Ph.D., Pharm. D., or M.D. degrees. 391 engaged primarily in research and development or technical operations, and 67 engaged in business development, finance, information systems, facilities, human resources, legal functions, or administrative support. We consider our employee relations to be good.

We are dedicated to conducting business with the highest standards of corporate responsibility. Our goal is to build a culture of diverse and passionate people striving to positively impact patients, our communities, and broader society. Our human capital resource priorities include attracting, recruiting, retaining, incentivizing and integrating our existing and new employees. We believe that a diverse, equitable, and inclusive workplace allows our company to best fulfill our mission. We are committed to continuing our efforts to increase diversity throughout our company and foster an inclusive work environment that supports our employees and the communities we serve. We have established a Diversity, Equity and Inclusion Committee that is working to amplify this focus at the company. In all the countries in which we operate, it is our policy to fully comply with all applicable laws regarding discrimination in the workplace. We are committed to recruiting the best people for the job regardless of gender, race, ethnicity, age, disability, sexual orientation, gender identity, cultural background, or religious belief.

The principal purposes of our comprehensive equity and cash compensation and benefits programs are to attract, motivate, retain, and reward new and existing employees. We do this by using a mix of compensation elements that balance achievement of our short-term goals with our long-term performance. In addition, employees are eligible to participate in our standard employee benefit plans, such as our retirement, health and welfare benefits plans, including medical, dental, and life and disability insurance plans. We

also offer our employees the opportunity to participate in a tax-qualified retirement plan, or the 401(k) Plan, and have the ability to make matching contributions under the 401(k) Plan, which is competitive with other companies in our industry.

We consider our human capital resources strategy to be comprehensive and is built around our core way of working: collaborative, undaunted, entrepreneurial, and results-oriented. We foster a strong relationship with and among our employees with ongoing efforts such as employee surveys, training and development programs, and other programs, including skill development courses, manager training, leadership development opportunities, tuition reimbursement and robust online course training libraries for reference on a myriad of development topics. We also support cross-functional career development pathways, in addition to traditional promotions within functions in the organization. We plan to continue to evolve and add to our suite of human capital resources as we grow.

Special Note About the Coronavirus Pandemic

The ongoing coronavirus pandemic continues to have unpredictable impacts on global societies, economies, financial markets, and business practices around the world. The extent and duration of such effects remain uncertain and difficult to predict, particularly as virus variants continue to spread. We are actively monitoring and managing our response and evaluating the actual and potential impacts to our business operations, including on our ongoing and planned clinical trials. We will continue to work closely with our third-party vendors, collaborators, and other parties in order to seek to advance our programs and pipeline of product candidates, while keeping the health and safety of our employees and their families, partners, third-party vendors, healthcare providers, patients and communities a top priority. For discussion regarding the impact of the coronavirus pandemic on our business and financial results, please refer to our “Risk Factors” in Part I, Item 1A and “Management's Discussion and Analysis of Financial Condition and Results of Operations” in Part II, Item 7 of this Annual Report on Form 10-K.

Information Available on the Internet

Investors and others should note that we announce material information to our investors using our investor relations website (https://crisprtx.gcs-web.com/), SEC filings, press releases, public conference calls and webcasts. We use these channels as well as social media to communicate with the public about our company, our business, our product candidates and other matters. It is possible that the information we post on social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the social media channels listed on our investor relations website. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act are available on our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC at its website (https://www.sec.gov).

Item 1A. Risk Factors.

This report contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those discussed in this report. Factors that could cause or contribute to these differences include, but are not limited to, those discussed below and elsewhere in this report and in any documents incorporated in this report by reference.

You should carefully consider the following risk factors, together with all other information in this report, including our financial statements and notes thereto, and in our other filings with the Securities and Exchange Commission. If any of the following risks, or other risks not presently known to us or that we currently believe to not be significant, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common shares could decline, and shareholders may lose all or part of their investment.

Risks Related to Our Financial Position and Need for Additional Capital

We Have Incurred Significant Operating Losses Since Our Inception And Anticipate That We Will Incur Continued Losses For The Foreseeable Future.

We have funded our operations through public and private offerings of our equity securities, private placements of our preferred shares, convertible loans and collaboration agreements with strategic partners. While we were profitable for the year ended December 31, 2021 due to an upfront payment associated with our collaboration with Vertex, we do not expect to be profitable in future years. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' deficit and working capital. We anticipate that our expenses will increase substantially if and as we:

- continue our clinical trials for our various programs;
- continue our current research programs and our preclinical and clinical development of product candidates;
- seek to identify additional research programs and additional product candidates;
- conduct IND supporting preclinical studies and initiate clinical trials for our product candidates;
- initiate preclinical studies and clinical trials for any other product candidates we identify and choose to develop;
- expand, maintain, enforce and/or defend our intellectual property estate;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- further develop our gene editing technology;
- hire additional clinical, quality control and scientific personnel;
- establish, expand or contract for manufacturing capabilities;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development;
- acquire or in-license other technologies; and,
- establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval.

As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing gene editing product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

We Will Need To Raise Substantial Additional Funding, Which Will Dilute Our Shareholders. If We Are Unable To Raise Capital When Needed, We Would Be Forced To Delay, Reduce Or Eliminate Some Of Our Product Development Programs Or Commercialization Efforts.

The development of gene editing product candidates is capital intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate preclinical studies and clinical trials for and seek marketing approval for our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Bayer, ViaCyte, Vertex or other future collaborators. We may also need to raise additional funds sooner if we choose to pursue additional indications

or geographies for our product candidates or otherwise expand more rapidly than we presently anticipate. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate certain of our research and development programs or future commercialization efforts.

As of December 31, 2022 and 2021, we had cash, cash equivalents and marketable securities of approximately $1,868.4 million and $2,379.1 million, respectively. With our cash, cash equivalents and marketable securities on hand as of December 31, 2022, we expect cash, cash equivalents and marketable securities to be sufficient to fund our current operating plan through at least the next 24 months.

Our future capital requirements will depend on, and could increase significantly as a result of, many factors, including:

- the scope, progress, results and costs of clinical trials, drug discovery, preclinical development, and laboratory testing for our wholly owned and partnered product candidates;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of establishing and maintaining a supply chain for the development and manufacture of our product candidates;
- the success of our collaborations with Vertex and ViaCyte;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any additional collaboration agreements we obtain;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs of fulfilling our obligations under the Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement to reimburse other parties for costs incurred in connection with the prosecution and maintenance of associated patent rights;
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of establishing or contracting for manufacturing capabilities if we obtain regulatory approvals to manufacture our product candidates;
- the costs of establishing or contracting for sales and marketing capabilities if we obtain regulatory approvals to market our product candidates; and
- our ability to establish and maintain healthcare coverage and adequate reimbursement.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. We cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our shareholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our shareholders and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborators or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidate, or be unable to expand our

operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

We Have A Limited Operating History, Which May Make It Difficult To Evaluate Our Technology And Product Development Capabilities And Predict Our Future Performance.

Our overall development efforts are ongoing and the first clinical trial for any of our product candidates was initiated at the end of 2018. Our programs require preclinical and clinical development; regulatory and marketing approval in multiple jurisdictions; obtaining manufacturing supply, capacity, and expertise; building of a commercial organization; substantial investment and significant marketing efforts before we generate any revenue from product sales. Our product candidates must be approved for marketing by the FDA or certain other health regulatory agencies, including the EMA, before we may commercialize any product.

Our limited operating history, particularly in light of the rapidly evolving gene editing field, may make it difficult to evaluate our technology and industry and predict our future performance. Our short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer. Similarly, we expect that our financial condition and operating results will fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. As a result, our shareholders should not rely upon the results of any quarterly or annual period as an indicator of future operating performance.

In addition, as a development stage company, we have encountered unforeseen expenses, difficulties, complications, delays and other known and unknown circumstances. As we advance our product candidates, we will need to continue to transition from a company with a research focus to a company capable of supporting clinical development and if successful, commercial activities. We may not be successful in such a transition.

Our Ability To Use Tax Loss Carryforwards In Switzerland May Be Limited.

Under Swiss law, we are entitled to carry forward losses we incur for a period of seven years and we can offset future profits, if any, against such losses. Tax losses are only finally assessed by the tax authorities when offset with taxable profit (which will not be the case if we are loss making). If not used, these tax losses will expire seven years after the year in which they occurred. Due to our limited income, there is a high risk that the tax loss carry forwards will expire partly or entirely and as a result they would not be applied to reduce future cash tax payments.

As of January 1, 2020, the Canton of Zug introduced its new law on the Swiss corporate tax reform. According to this new law, the ordinary effective corporate income tax rate amount was reduced to 11.91% (federal, cantonal and communal) in 2020 and was subsequently reduced to 11.85% in 2021.

Risks Related to Our Business, Technology and Industry

If We Are Unable To Advance Our Product Candidates To Clinical Development, Obtain Regulatory Approval And Ultimately Commercialize Our Product Candidates, Or Experience Significant Delays In Doing So, Our Business Will Be Materially Harmed.

Our development efforts are ongoing and have focused our research and development efforts to date on CRISPR/Cas9, gene editing technology, and our initial product candidates. Our future success depends heavily on the successful development of our CRISPR/Cas9 gene editing product candidates. We have invested substantially all of our efforts and financial resources in the identification and development of our current product candidates. Our ability to generate product revenue will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. For example, our research programs, including those subject to our collaboration agreements with Vertex and ViaCyte and option agreement with Bayer, may fail to identify potential product candidates for clinical development for a number of reasons or may fail to successfully advance any product candidates through clinical development. Our potential product candidates, or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the product candidates impractical to manufacture, unmarketable, or unlikely to receive marketing approval. We currently generate no revenue from sales of any product and we may never be able to develop or commercialize a marketable product.

We must file U.S. Investigational New Drug, or IND, applications, clinical trial applications, or CTAs, or their equivalents with regulatory authorities to commence clinical trials. The filing of CTAs or INDs for any product candidate is subject to the identification and selection of one or more guide RNAs with acceptable efficiency, among other activities. In addition, commencing any future clinical trial is also subject to acceptance by the European regulatory authorities, or its equivalent, of our CTAs, or the FDA of our INDs, and finalizing the trial design based on discussions with the applicable regulatory authorities. In the event that the European regulatory authorities, FDA or their equivalent requires us to complete additional preclinical studies or we are required to satisfy other requests, our clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, they

could disagree that we have satisfied their requirements to commence our clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter approval conditions than we currently expect.

To become and remain profitable, we must develop and commercialize product candidates with significant market potential, which will require us to be successful in a range of challenging activities. Our product candidates require preclinical and clinical development; regulatory and marketing approval in multiple jurisdictions; obtaining manufacturing supply, capacity, and expertise; building of a commercial organization; substantial investment and significant marketing efforts before we generate any revenue from product sales. In addition, our product development programs must be approved for marketing by the FDA, EMA or certain other health regulatory agencies, before we may commercialize our product candidates. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease our value and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in our value also could cause shareholders to lose all or part of their investment.

The success of our product candidates will depend on several factors, including the following:

- successful completion of clinical trials and preclinical studies;
- sufficiency of our financial and other resources to complete the necessary clinical trials and preclinical studies;
- ability to develop safe and effective delivery mechanisms for our *in vivo* therapeutic programs;
- ability to identify optimal RNA sequences to guide genomic editing;
- maintenance of current, and entry into additional, collaborations to further the development of our product candidates;
- approval of CTAs or INDs for our product candidates to commence clinical trials;
- successful enrollment in, and completion of, clinical trials and preclinical studies;
- successful data from our clinical program that support an acceptable risk-benefit profile of our product candidates for the intended patient populations;
- receipt of regulatory and marketing approvals from applicable regulatory authorities;
- establishing and maintaining arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- successful development of our internal manufacturing processes and transfer to larger-scale facilities operated by either a contract manufacturing organization or by us;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;
- effective competition with other therapies and treatment options;
- establishment and maintenance of healthcare coverage and adequate reimbursement;
- enforcement and defense of intellectual property rights and claims;
- maintenance of a continued acceptable safety profile of the product candidates following approval; and
- achieving desirable medicinal properties for the intended indications.

Additionally, because our technology involves gene editing across multiple cell and tissue types, we are subject to many of the challenges and risks that gene therapies face, including:

- regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future; to date a limited number of products that involve the genetic modification of patient cells have been approved in the United States and the EU;
- the administration processes or related procedures for our product candidates (e.g., treatment with myeloablative busulfan conditioning prior to receiving exa-cel or undergoing a lymphodepletion regimen prior to receiving our immunotherapy product candidates);

- improper insertion of a gene sequence into a patient's chromosome could lead to lymphoma, leukemia or other cancers, or other aberrantly functioning cells; and
- the FDA recommends a follow-up observation period of 15 years or longer for all patients who receive treatment using gene therapies, and we may need to adopt and support, and have adopted and are supporting for certain of our trials, such an observation period for our product candidates.

If we do not succeed in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

Our CRISPR/Cas9 Gene Editing Product Candidates Are Based On A Relatively New Gene Editing Technology, Which Makes It Difficult To Predict The Time And Cost Of Development And Of Subsequently Obtaining Regulatory Approval, If At All. There Have Only Been A Limited Number Of Clinical Trials Of Product Candidates Based On Gene Editing Technology And No Gene Editing Products Have Been Approved In The United States Or In The EU.

CRISPR/Cas9 gene editing technology is relatively new, and no products based on CRISPR/Cas9 or other similar gene editing technologies have been approved in the United States or the EU and only a limited number of clinical trials of product candidates based on gene editing technologies have been commenced. As such it is difficult to accurately predict the developmental challenges we may incur for our product candidates as they proceed through product discovery or identification, preclinical studies and clinical trials. For example, because we have only limited data from clinical trials in exa-cel, CTX110 and CTX130, we have not yet been able to fully assess safety in humans. In addition, because we have only recently commenced clinical trials for certain of our other product candidates, we have not yet been able to assess safety in humans. There may be long-term effects from treatment with any product candidates that we develop that we cannot predict at this time. Any product candidates we may develop will act at the level of DNA, and, because animal DNA differs from human DNA, testing of our product candidates in animal models may not be predictive of the results we observe in human clinical trials of our product candidates for either safety or efficacy. Also, animal models may not exist for some of the diseases we choose to pursue in our programs. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our gene editing technology, or any similar or competitive gene editing technologies, will result in the identification, development, and regulatory approval of any products. There can be no assurance that any development problems we experience in the future related to our gene editing technology or any of our research and development programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. Any of these factors may prevent us from completing our preclinical studies or any clinical trials that we may initiate or commercializing any product candidates we may develop on a timely or profitable basis, if at all.

The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. No products based on gene editing technologies have been approved by regulators. As a result, the regulatory approval process for product candidates such as ours is uncertain and may be more expensive and take longer than the approval process for product candidates based on other, better known or more extensively studied technologies. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the EU or how long it will take to commercialize our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product candidate to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects may be harmed.

Our Engineered Allogeneic T cell Product Candidates Represent A Novel Approach To Cancer Treatment That Creates Significant Challenges For Us.

For our immuno-oncology programs, we are developing a pipeline of allogeneic T cell product candidates (including, for example, CTX110, CTX112, CTX130 and CTX131) that are engineered from healthy donor T cells to express chimeric antigen receptors, or CARs, and are intended for use in any patient with certain cancers. Unlike for autologous CAR T therapies, for allogeneic CAR T therapies, we are reliant on receiving healthy donor material to manufacture our product candidates. Healthy donor T cells vary in type and quality, and this variation makes producing standardized allogeneic CAR T product candidates challenging and makes the development and commercialization pathway of those product candidates uncertain.

We have developed screening processes designed to enhance the quality and consistency of T cells used in the manufacture of our CAR T cell product candidates, but our screening processes may fail to identify suitable donor material and we may discover failures with the material after production. We may also have to update our specifications for new risks that may emerge, such as to screen for new viruses.

We have strict specifications for donor material, which include specifications required by regulatory authorities. If we are unable to identify and obtain donor material that satisfy specifications, agree with regulatory authorities on appropriate specifications, or address variability in donor T cells, there may be inconsistencies in the product candidates we produce or we may be unable to

initiate or continue ongoing clinical trials on the timelines we expect, which could harm our reputation and adversely impact our business and prospects.

In addition, approved autologous CAR T therapies and those under development have shown frequent rates of cytokine release syndrome, neurotoxicity, serious infections, prolonged cytopenia and hypogammaglobulinemia, and other serious adverse events that have resulted in patient deaths. We expect similar adverse events for our allogeneic CAR T product candidates. Moreover, patients eligible for allogeneic CAR T cell therapies but ineligible for autologous CAR T cell therapies due to aggressive cancer and inability to wait for autologous CAR T cell therapies may be at greater risk for complications and death from therapy. Our allogeneic CAR T cell product candidates may also cause unique adverse events related to the differences between the donor and patients, such as Graft versus Host Disease, or GvHD, or infusion reactions. GvHD results when allogeneic T cells start recognizing the patient's normal tissue as foreign.

We have designed our CRISPR/Cas9 gene editing technology to eliminate the T-cell receptor from the healthy donor T cells to reduce the risk of GvHD from our product candidates, as well as to remove the class I major histocompatibility complex from the cell surface in order to limit the patient's immune system from attacking the allogeneic T cells and to improve the persistence of the CAR T cells. However, the gene editing of our product candidates may not be successful in limiting the risk of GvHD or premature rejection by the patient. In addition, results of our immuno-oncology clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics.

If significant GvHD or other adverse events are observed with the administration of our product candidates, or if any of the product candidates is viewed as less safe or effective than autologous therapies or other allogenic therapies, our ability to develop allogeneic therapies may be adversely affected.

The FDA, The NIH 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, Which May Be Difficult To Predict.

The FDA, NIH and the EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates.

Regulatory requirements in the United States and in other jurisdictions governing gene therapy products have changed frequently and may continue to change in the future. The FDA has issued several guidance documents on gene therapy products. The FDA established the Office of Therapeutic Products within its Center for Biologics Evaluation and Research to consolidate the review of gene therapy and related products, and established the Cellular, Tissue and Gene Therapies Advisory Committee to advise this review. In addition to the government regulators, the IBC and IRB of each institution at which we conduct clinical trials of our product candidates, or a central IRB if appropriate, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy product candidates conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the EMA governs the development of gene therapies in the EU and may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines. These regulatory review agencies and committees and the new requirements or guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies or trials, 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. As we advance our product candidates and seek regulatory approval, we will be required to consult with these regulatory agencies and committees and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all.

If Any Of The Product Candidates We May Develop Or Administration Processes We Rely On Causes Undesirable Side Effects, It Could Delay Or Prevent Their Regulatory Approval, Limit The Commercial Potential Or Result In Significant Negative Consequences Following Any Potential Marketing Approval.

Product candidates we may develop may be associated with undesirable or unacceptable side effects, unexpected characteristics or other serious adverse events, including death or off-target cuts of DNA, or the introduction of cuts in DNA at locations other than the target sequence. These off-target cuts could lead to disruption of a gene or a genetic regulatory sequence at an unintended site in the DNA, or, in those instances where we also provide a segment of DNA to serve as a repair template, it is possible that following

off-target cut events, DNA from such repair template could be integrated into the genome at an unintended site, potentially disrupting another important gene or genomic element.

There also is the potential risk of delayed adverse events following exposure to gene editing therapy due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. Possible adverse side effects that could occur with treatment with gene editing products include an immunologic reaction after administration which could substantially limit the effectiveness of the treatment.

Immunotherapy, and its method of action of harnessing the body's immune system, is powerful and could lead to serious side effects that we only discover in clinical trials. Unforeseen side effects could arise either during clinical development or, if such side effects are rare, after our product candidates have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. If our CRISPR/Cas9 gene editing technology demonstrates a similar effect, we may decide or be required to halt or delay preclinical development or clinical development of our product candidates.

In addition to serious adverse events or side effects caused by any product candidate we may develop, the administration process or related procedures also can cause undesirable side effects. Patients who enroll in our exa-cel clinical trials have their own CRISPR/Cas9 edited-hematopoietic stem and progenitor cells, exa-cel, infused back into the patient as part of a stem cell transplant, a process which involves, among other things, a patient being treated with myeloablative busulfan conditioning. Patients undergoing stem cell transplants may also encounter side effects (ranging from mild to severe) that are unrelated to the administration of exa-cel. Patients who enroll in our immunotherapy trials undergo a lymphodepletion regimen, which generally includes fludarabine and cyclophosphamide that may cause serious adverse events. Because these regimens will cause a transient and sometimes prolonged immune suppression, patients will have an increased risk of certain infections that may be unable to be cleared by the patient and could ultimately lead to death. Any side effects may not be appropriately recognized or managed by the treating medical staff. We or our collaborators expect to have to educate medical personnel using any product candidates we may develop to understand the side effect profiles for our clinical trials and upon any commercialization of such product candidates. Inadequate recognition or management of the potential side effects of such product candidates could result in patient injury or death. If any undesirable or unacceptable side effects, unexpected characteristics or other serious adverse events occur, our clinical trials or commercial distribution of any product candidates or products we develop alone or with collaborators could be suspended or terminated, and our business and reputation could suffer substantial harm.

If in the future we are unable to demonstrate that such adverse events were caused by factors other than our product candidate, the FDA, EMA or other comparable health regulatory authorities could order us to cease further clinical studies of, or deny approval of, any product candidates we are able to develop for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any product candidate, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to identify and develop product candidates, and may harm our business, financial condition, result of operations and prospects significantly.

Additionally, if we successfully develop a product candidate and it receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits of treatment with such product candidate outweighs the risks for each potential patient, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, extensive patient monitoring, or distribution systems and processes that are highly controlled, restrictive, and more costly than what is typical for the industry. Furthermore, if we or others later identify undesirable side effects caused by any product candidate that we develop, several potentially significant negative consequences could result, including:

- regulatory authorities may revoke licenses or suspend, vary or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Moreover, gene therapy product candidates investigated by other parties have resulted in serious adverse events, including deaths, and it is possible that the FDA or other regulatory authorities could impose a clinical hold on clinical trials of our product candidates after becoming aware of adverse events with products or product candidates in the same class as our product candidates.

Any of these events could prevent us from achieving or maintaining market acceptance of our gene editing technology and any product candidates we may identify and develop and could have a material adverse effect on our business, financial condition, results of operations and prospects.

If We Experience Delays Or Difficulties In The Enrollment Of Patients In Clinical Trials, Our Receipt Of Necessary Regulatory Approvals Could Be Delayed Or Prevented.

We or our collaborators may not be able to initiate or continue clinical trials for any product candidates we identify or develop if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States, or as needed to provide appropriate statistical power for a given trial. Enrollment may be particularly challenging for any rare genetically defined diseases we may target in the future. In addition, if patients are unwilling to participate in our gene editing trials because of negative publicity from adverse events related to the biotechnology, gene therapy or gene editing fields, competitive clinical trials for similar patient populations, clinical trials with competing products, or for other reasons, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of any product candidates we may develop may be delayed. Moreover, some of our competitors may have ongoing clinical trials for product candidates that would treat the same indications as any product candidates we may develop, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- availability of eligible prospective patients that are otherwise eligible patients for competitive clinical trials;
- availability and efficacy of approved medications for the disease under investigation;
- availability of genetic testing for potential patients;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- eligibility and exclusion criteria for the trial in question;
- perceived risks and benefits of the product candidate under trial;
- perceived risks and benefits of gene editing and cellular therapies as therapeutic approaches;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- the ongoing coronavirus pandemic.

Enrollment delays in our clinical trials may result in increased development costs for any product candidates we may develop, which would cause our value to decline and limit our ability to obtain additional financing. If we or our collaborators have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit, or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations, and prospects.

Our Business May Be Adversely Affected By A Pandemic, Epidemic Or Outbreak Of An Infectious Disease, Such As The Ongoing Coronavirus Pandemic And The Emergence of Additional Variants.

Our business could be adversely affected by health epidemics in regions where we have concentrations of clinical trial sites or other business activities and could cause significant disruption in the operations of third-party contract manufacturers and contract research organizations upon whom we rely, as well as our ability to recruit patients for our clinical trials. For example, the ongoing coronavirus pandemic continues to have unpredictable impacts on global societies, economies, financial markets, and business practices around the world.

The extent to which the ongoing coronavirus pandemic may impact our business, results of operations and future growth prospects will depend on a variety of factors and future developments, which are highly uncertain and cannot be predicted with confidence, including the duration, scope and severity of the pandemic, particularly as virus variants continue to spread. For example, we experienced, and may experience again, some temporary delays or disruptions due to the coronavirus pandemic, including pauses in and delays to patient dosing, limited or reduced patient access to ICU beds, hospitals and healthcare resources generally, delayed

initiation of new clinical trial sites and limited on-site personnel support at various trial sites. In addition, certain of our third-party manufacturers and suppliers paused their operations in the early stages of the pandemic, and some have paused their operations again as additional waves of the coronavirus pandemic have impacted local communities and/or as a result of national and local regulations.

We are actively monitoring and managing our response and evaluating the actual and potential impacts to our business operations, including on our ongoing and planned clinical trials. We will continue to work closely with our third-party vendors, collaborators, and other parties in order to seek to advance our programs and pipeline of product candidates, while keeping the health and safety of our employees and their families, partners, third-party vendors, healthcare providers, patients and communities a top priority.

Positive Results From Early Preclinical Studies Or Preliminary Results from Clinical Trials Of Our Product Candidates Are Not Necessarily Predictive Of The Results Of Later Preclinical Studies And Any Future Clinical Trials Of Our Product Candidates. If We Cannot Replicate The Positive Results From Our Earlier Preclinical Studies Of Our Product Candidates In Our Later Preclinical Studies, Clinical Trials And Future Clinical Trials, We May Be Unable To Successfully Develop, Obtain Regulatory Approval For And Commercialize Our Product Candidates.

Any positive results from our preclinical studies or preliminary results from our clinical trials of our product candidates may not necessarily be predictive of the results from required later preclinical studies and clinical trials. Preliminary, interim and top-line data from clinical trials may change as more patient data become available. Preliminary, interim or top-line data from clinical trials are not necessarily predictive of final results, including the results submitted in support of approval in a BLA or equivalent submission outside the United States. Interim, top-line and preliminary data remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously announced. As a result, preliminary, interim and top-line data should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the interim data could significantly harm our business prospects. Moreover, preliminary, interim and top-line data are subject to the risk that one or more of the clinical outcomes may materially change as more patient data become available when patients mature on study, patient enrollment continues or as other ongoing or future clinical trials with a product candidate further develop. For example, consistent with the FDA's recommendation, certain of our clinical trials include a 15 year follow-up observation period in which we will continue to collect patient data.

The information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically more extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. Any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. Similarly, even if we are able to complete our planned preclinical studies or any future clinical trials of our product candidates according to our current development timeline, the positive results from such preclinical studies and clinical trials of our product candidates may not be replicated in subsequent preclinical studies or clinical trial results.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development and we cannot be certain that we will not face similar setbacks. Similarly, many companies in the pharmaceutical and biotechnology industries have failed to receive regulatory approval despite completing registration trials. These setbacks have been caused by, among other things, preclinical and other nonclinical findings made while clinical trials were underway or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. Moreover, preclinical, nonclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval.

Even If We Complete The Necessary Preclinical Studies And Clinical Trials, The Marketing Approval Process Is Expensive, Time-Consuming, And Uncertain And May Prevent Us From Obtaining Approvals For The Commercialization Of Any Product Candidates We May Develop. If We Are Not Able To Obtain, Or If There Are Delays In Obtaining, Required Regulatory Approvals, We Will Not Be Able To Commercialize, Or Will Be Delayed In Commercializing, Product Candidates We May Develop, And Our Ability To Generate Revenue Will Be Materially Impaired.

Any product candidates we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States, by EMA in the EU and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. While we have multiple product candidates in clinical development and advanced preclinical development for a range of diseases, we have not yet submitted BLAs for any of our wholly-owned allogeneic CAR T product candidates to the FDA, or similar marketing applications to comparable foreign authorities. In the fourth quarter of 2022, we and Vertex completed regulatory submissions for exa-cel with the EMA and MHRA in the EU and the UK, respectively, for the potential treatment of SCD and TDT, and both the EMA and the MHRA have validated the respective Marketing Authorization

Applications. In addition, we and Vertex initiated the BLA rolling submission to the FDA in November 2022, which we and Vertex expect to be complete by the end of the first quarter of 2023. However, we have not received approval or clearance to market any product candidates from regulatory authorities in any jurisdiction and it is possible that none of our product candidates or any product candidates we may seek to develop, alone or in conjunction with collaborators, in the future will ever obtain regulatory approval or clearance.

We have limited experience in submitting and supporting the applications necessary to gain regulatory and marketing approvals. We expect to rely on third-party CROs and/or regulatory consultants to assist us in this process for our wholly-owned product candidates and, pursuant to our A&R Vertex JDCA, we have relied on Vertex for submitting such applications for our hemoglobinopathies product candidates. Submission of a BLA or other similar marketing applications to comparable foreign authorities and securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity, efficacy and potency, also known as safety and effectiveness, for each desired therapeutic indication. A BLA must also include significant information regarding the chemistry, manufacturing and controls for the product candidate. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Should the FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel as a result of the coronavirus pandemic, the FDA has stated that it generally intends to issue a complete response letter or defer action on the application until an inspection can be completed.

In general, the FDA requires the successful completion of two pivotal trials to support approval of a BLA, but in certain circumstances, will approve a BLA based on only one pivotal trial; and our ability to submit and obtain approval of a BLA is ultimately an FDA review decision, which will be dependent upon the data available at such time, and the available data may not be sufficiently robust from a safety and/or efficacy perspective to support the submission or approval of a BLA. For example, there is no assurance that data obtained at the completion of any of our clinical trials, including for our ongoing wholly-owned product candidates, including CTX110 and CTX130, will indicate clinically meaningful benefit or support submission of a BLA, or will be sufficiently robust from a safety and/or efficacy perspective to support either accelerated or conditional approval or full approval. Moreover, there is no assurance that the data obtained to date in the ongoing CLIMB-111 and CLIMB-121 clinical trials of exa-cel and being submitted to the FDA on a rolling basis will be sufficiently robust from a safety and/or efficacy perspective to support either accelerated or conditional approval or full approval of a BLA. Depending on the outcome of these ongoing clinical trials, and robustness of the data submitted, once submitted, the FDA may require that we conduct additional or larger pivotal trials before we can submit or obtain approval of a BLA. Furthermore, if any undesirable or unacceptable side effects, unexpected characteristics or other serious adverse events occur, and if we are unable to demonstrate such adverse events were caused by factors other than our product candidate, the FDA, EMA or other comparable health regulatory authorities could suspend our clinical trial until we are able to gather sufficient information or order us to cease further clinical studies of our product candidate. If this were to occur this would likely result in delays in our ability to submit a BLA for regulatory approval. We may face similar challenges with foreign regulatory bodies.

Furthermore, failure of one or more clinical trials can occur at any stage in the clinical trial process. Any product candidates we develop may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Accordingly, the regulatory pathway for our product candidates is still uncertain, complex, and lengthy, and ultimately, approval may not be obtained. Even if our product candidates demonstrate safety and efficacy in clinical studies, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development.

The process of obtaining marketing approvals, both in the United States and in other foreign jurisdictions, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity, and novelty of the product candidates involved. 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. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any product candidates we may develop, the commercial prospects for those product candidates may be harmed, and our ability to generate revenues will be materially impaired.

We May Never Obtain FDA Approval For Any Of Our Product Candidates In The United States, And Even If We Do, We May Never Obtain Approval For Or Commercialize Any Of Our Product Candidates In Any Other Jurisdiction, Which Would Limit Our Ability To Realize Their Full Market Potential.

In order to eventually market any of our product candidates in any particular jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a jurisdiction-by-jurisdiction basis regarding safety and efficacy. Approval by the FDA in the United States, if obtained, does not ensure approval by regulatory authorities in other countries or jurisdictions. Similarly, approval by foreign regulatory authorities does not ensure approval by the FDA. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking regulatory approval in multiple jurisdictions could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time-consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in certain countries. Regulatory approval processes outside the United States involve all of the risks associated with FDA approval. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and, as a company, do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products will be unrealized.

Breakthrough Therapy Designation, Fast Track Designation, Regenerative Medicine Advanced Therapy Designation or Priority Review by the FDA, or PRIME Scheme by the EMA, Even If Granted for Any of Our Product Candidates, May Not Lead to a Faster Development, Regulatory Review or Approval Process, and It May Not Increase the Likelihood That Any of Our Product Candidates Will Receive Marking Approval.

We may seek a Breakthrough Therapy Designation for some of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA may also be eligible for priority review and accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

We have obtained and may seek Fast Track Designation for some of our product candidates. For instance, exa-cel has been granted Fast Track Designation by the FDA for the treatment of TDT and SCD. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation; we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's marketing application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the application is submitted. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Fast Track Designation alone does not guarantee qualification for the FDA's priority review procedures.

We have obtained and may seek RMAT designation for some of our product candidates. For instance, exa-cel has been granted RMAT designation by the FDA for the treatment of TDT and SCD, as well as CTX110 for the treatment of relapsed or refractory B-cell lymphoma and CTX130 for the treatment of Mycosis Fungoides and Sézary Syndrome (MF/SS). In 2017, the FDA established the RMAT designation as part of its implementation of the 21st Century Cures Act to expedite review of any drug that meets the following criteria: it qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and preliminary clinical evidence indicates that the drug has the

potential to address unmet medical needs for such a disease or condition. Like Breakthrough Therapy Designation, RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. There can be no assurance that the FDA would allow any of the product candidates we may develop to proceed on an accelerated approval pathway, and even if the FDA did allow such pathway, there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy. There is no assurance that we will be able to obtain RMAT designation for other of our product candidates. RMAT designation does not change the FDA's standards for product approval, and there is no assurance that such designation will result in expedited review or approval or that the approved indication will not be narrower than the indication covered by the designation. Additionally, RMAT designation can be revoked if the criteria for eligibility cease to be met as clinical data emerges. Further, even if we received accelerated approval, any post-approval studies required to confirm and verify clinical benefit may not show such benefit, which could lead to withdrawal of any approvals we have obtained. Receiving accelerated approval does not assure that the product's accelerated approval will eventually be converted to a traditional approval. Moreover, under FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of approval for a product granted accelerated approval. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. FDORA also gives the FDA increased authority to withdraw approval of a drug or biologic granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

Finally, we have obtained and may seek to qualify our product candidates under the PRIME scheme from the EMA. For instance, exa-cel has been granted PRIME designation for the treatment of TDT and SCD. The PRIME scheme is open to medicines under development and for which the applicant intends to apply for an initial MAA through the centralized procedure. Eligible products must target conditions for which where is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods or therapy or improving existing ones. There is no assurance that we will be able to obtain PRIME qualification for other of our product candidates. PRIME does not change the standards for product approval, and there is no assurance that such qualification will result in expedited review or approval. Moreover, where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

We May Seek Designation For Our Platform Technology As A Designated Platform Technology, But We Might Not Receive Such Designation, And Even If We Do, Such Designation May Not Lead To A Faster Regulatory Review Or Approval Process.

We may seek designation for our platform technology as a designated platform technology. Under the Food and Drug Omnibus Reform Act of 2022 ("FDORA"), a platform technology incorporated within or utilized by a drug or biological product is eligible for designation as a designated platform technology if (1) the platform technology is incorporated in, or utilized by, a drug approved under a BLA; (2) preliminary evidence submitted by the sponsor of the approved or licensed drug, or a sponsor that has been granted a right of reference to data submitted in the application for such drug, demonstrates that the platform technology has the potential to be incorporated in, or utilized by, more than one drug without an adverse effect on quality, manufacturing, or safety; and (3) data or information submitted by the applicable person indicates that incorporation or utilization of the platform technology has a reasonable likelihood to bring significant efficiencies to the drug development or manufacturing process and to the review process. A sponsor may request the FDA to designate a platform technology as a designated platform technology concurrently with, or at any time after, submission of an IND application for a drug that incorporates or utilizes the platform technology that is the subject of the request. If so designated, the FDA may expedite the development and review of any subsequent original BLA for a drug that uses or incorporates

the platform technology. Even if we believe our platform technology meets the criteria for such designation, the FDA may disagree and instead determine not to grant such designation. In addition, the receipt of such designation for a platform technology does not ensure that a drug will be developed more quickly or receive FDA approval. Moreover, the FDA may revoke a designation if the FDA determines that a designated platform technology no longer meets the criteria for such designation.

We May Be Unable To Obtain Orphan Drug Designation Or Exclusivity. If Our Competitors Are Able To Obtain Orphan Drug Exclusivity For Products That Constitute The Same Drug And Treat The Same Indications As Our Product Candidates, We May Not Be Able To Have Competing Products Approved By The Applicable Regulatory Authority For A Significant Period Of Time.

We have received orphan drug designation in the United States from the FDA for certain of our programs, including for CTX130 for the treatment of T-cell lymphomas. We also have received orphan drug designation from the FDA and the European Commission for exa-cel for the treatment of TDT and SCD. We may in the future seek orphan drug designation for certain of our other product candidates, but we may be unable to maintain orphan drug designation or obtain any benefits associated with orphan drug designation, including market exclusivity. Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs and biologics intended to treat relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is defined as a disease or condition having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the European Commission after recommendation from the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product. An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and in the European Union the ability to apply for a centralized EU marketing authorization.

Certain of our current product candidates and our future product candidates may target patient populations that are smaller than the numbers described above. If we request orphan drug designation for our product candidates, there can be no assurances that FDA or the European Commission will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the European Commission from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the United States can be extended by six months if the sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The exclusivity period in the European Union can be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, because, for example, the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug, including if it is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or

- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

There is no assurance that we will be able to obtain orphan drug designation for other of our other product candidates. Orphan drug designation does not change the standards for product approval, and there is no assurance that such designation will result in expedited review or approval.

Adverse Public Perception Of Gene Editing And Cellular Therapy Products May Negatively Impact Demand For, Or Regulatory Approval Of, Our Product Candidates.

Our product candidates involve editing the human genome. The clinical and commercial success of our product candidates will depend in part on public acceptance of the use of gene editing therapies for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene editing is unsafe, unethical, or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy in general could result in greater government regulation and stricter labeling requirements of gene editing products, including any of our product candidates, and could cause a decrease in the demand for any products we may develop. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

In particular, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns relating to the application of gene editing technology to human embryos or the human germline. For example, in April 2016, a group of scientists reported on their attempts to edit the genome of human embryos to modify the gene for hemoglobin beta. This is the gene in which a mutation occurs in patients with the inherited blood disorder beta thalassemia. Although this research was purposefully conducted in embryos that were not viable, the work prompted calls for a moratorium or other types of restrictions on gene editing of human eggs, sperm, and embryos. Additionally, in November 2018, Dr. Jiankui He, a biophysics researcher who was an associate professor in the Department of Biology of the Southern University of Science and Technology in Shenzhen, China, reportedly claimed he had created the first human genetically edited babies, twin girls. This claim, and another that Dr. He had helped create a second gene-edited pregnancy, was subsequently confirmed by Chinese authorities and was negatively received by the public, in particular by those in the scientific community. News reports indicate that Dr. He was sentenced to three years in prison and fined $430,000 in December 2019 by the Chinese government for illegal medical practice in connection with such activities. In the wake of the claim, the World Health Organization established a new advisory committee to create global governance and oversight standards for human gene editing. The Alliance for Regenerative Medicine in Washington, D.C. has called for a voluntary moratorium on the use of gene editing technologies, including CRISPR/Cas9, in research that involves altering human embryos or human germline cells and has also released principles for the use of gene editing in therapeutic applications endorsed by a number of companies that use gene editing technologies. Similarly, the NIH has announced that it would not fund any use of gene editing technologies in human embryos, noting that there are multiple existing legislative and regulatory prohibitions against such work, including the Dickey-Wicker Amendment, which prohibits the use of appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. Laws in the United Kingdom prohibit genetically modified embryos from being implanted into women, but embryos can be altered in research labs under license from the Human Fertilisation and Embryology Authority. Research on embryos is more tightly controlled in many other European countries.

Although we do not use our technologies to edit human embryos or the human germline, such public debate about the use of gene editing technologies in human embryos and heightened regulatory scrutiny could prevent or delay our development of product candidates. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair our development and commercialization of product candidates or demand for any products we may develop. Adverse events in our preclinical studies or clinical trials or those of our competitors or of academic researchers utilizing gene editing technologies, even if not ultimately attributable to product candidates we may identify and develop, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of potential product candidates we may identify and develop, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product candidates.

If We Are Unable To Establish Sales And Marketing Capabilities Or Enter Into Agreements With Third Parties To Sell And Market Products Based On Our Technologies, We May Not Be Successful In Commercializing Our Products If And When Any Products Candidates Are Approved And We May Not Be Able To Generate Any Revenue.

We do not currently have a sales or marketing infrastructure and, as a company, have no experience in the sale, marketing or distribution of therapeutic products. To achieve commercial success for any approved product candidate for which we retain sales and marketing responsibilities, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates, if any are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell any product candidates that we develop ourselves. For example, pursuant to our A&R Vertex JDCA, Vertex has the right to conduct all commercialization activities relating to exa-cel throughout the world and net profits and net losses, as applicable, incurred under the A&R Vertex JDCA are allocated 40% to CRISPR and 60% to Vertex. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates. Further, our business, results of operations, financial condition and prospects will be materially adversely affected.

Even If We, Or Any Collaborators We May Have, Obtain Marketing Approvals For Any Product Candidates We Develop, The Terms Of Approvals And Ongoing Regulation Of Our Products Could Require The Substantial Expenditure Of Resources And May Limit How We, Or They, Manufacture And Market Our Products, Which Could Materially Impair Our Ability To Generate Revenue.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, current Good Manufacturing Practice, or cGMP, requirements relating to quality control, quality assurance and corresponding maintenance of records and documents and requirements regarding recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. The FDA also may place other conditions on approvals including the requirement for a REMS to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the BLA, must submit a proposed REMS before it can obtain approval. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

Accordingly, assuming we, or any collaborators we may have, receive marketing approval for one or more product candidates we develop, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, and quality control. In addition, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could have the marketing approvals for our products withdrawn by regulatory authorities and our, or such collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our business, operating results, financial condition, and prospects.

Any Product Candidate For Which We, Or Any Collaborators We May Have, Obtain Marketing Approval Could Be Subject To Restrictions Or Withdrawal From The Market, And We Or They May Be Subject To Substantial Penalties If We Or They Fail To Comply With Regulatory Requirements Or If We Or They Experience Unanticipated Problems With Our Products, When And If Any Of Them Are Approved.

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of biologics to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we, or any collaborators we may have, do not market our products for their approved indications, we or they may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the United States Department of Justice. Violation of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown problems with a product candidate, including adverse events of unanticipated severity or frequency, or with our or other collaborators' manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on such products, manufacturers, or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on the distribution or use of a product;
- requirements to conduct post-marketing clinical trials;
- receipt of warning or untitled letters;
- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory biologic recalls;
- refusal to approve pending applications or supplements to approved applications that we or our collaborators submit;
- fines, restitution, or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals or revocation of biologics licenses;
- suspension of any ongoing clinical trials;
- refusal to permit the import or export of our products;
- product seizure or detention; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, we or our collaborators may lose any marketing approval that we or our collaborators may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

Any government investigation of alleged violations of law, including investigations of any of our vendors, could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may also inhibit our or our collaborators' ability to commercialize any product candidates we may develop and adversely affect our business, financial condition, results of operations, and prospects.

The Commercial Success Of Any Of Our Product Candidates Will Depend Upon Its Degree Of Market Acceptance By Physicians, Patients, Third-party Payors And Others In The Medical Community.

Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our products. Even with the requisite approvals from FDA in the United States, the EMA in the EU and other regulatory authorities internationally, the commercial success of our product candidates will depend, in significant part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidates in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and

others in the medical community. The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy, durability and safety of such product candidates as demonstrated in any future clinical trials;
- the potential and perceived advantages of product candidates over alternative treatments;
- the cost of treatment relative to alternative treatments;
- the clinical indications for which the product candidate is approved by FDA, the EMA or other regulatory authorities;
- patient awareness of, and willingness to seek, genotyping;
- the willingness of physicians to prescribe new therapies;
- the willingness of the target patient population to try new therapies;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of FDA, the EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party payor coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and future clinical trials, market acceptance of the product will not be fully known until after it is launched. If our product candidates do not achieve an adequate level of acceptance following regulatory approval, if ever, we may not generate significant product revenue and may not become profitable.

We Face Significant Competition In An Environment Of Rapid Technological Change, And The Possibility That Our Competitors May Achieve Regulatory Approval Before Us Or Develop Therapies That Are More Advanced Or Effective Than Ours, Which May Harm Our Business And Financial Condition And Our Ability To Successfully Market Or Commercialize Our Product Candidates.

The biotechnology and pharmaceutical industries, including in the gene editing, gene therapy and cell therapy fields, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property and proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we currently face, and will continue to face, substantial competition from many different sources, including large pharmaceutical, specialty pharmaceutical and biotechnology companies; academic institutions and governmental agencies; and public and private research institutions, some or all of which may have greater access to capital or resources than we do. For any products that we may ultimately commercialize, not only will we compete with any existing therapies and those therapies currently in development, but we will also have to compete with new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that utilize technologies encompassing genomic medicines to create therapies, including gene editing, gene therapy and cell therapy. In addition, we compete with companies working to develop therapies in areas related to our specific research and development programs.

Our platform and product focus is on the development of therapies using CRISPR/Cas9 gene editing technology. We are aware of several companies focused on developing therapies in various indications using CRISPR/Cas9 gene editing technology, including Intellia Therapeutics and Editas Medicine. In addition, several academic groups have developed new gene editing technologies based on CRISPR/Cas9, such as base editing and prime editing, that may have utility in therapeutic development. Companies seeking to develop therapies based on these technologies include Beam Therapeutics and Prime Medicine

There are also companies developing therapies using additional gene editing technologies, such as TALENs, meganucleases and ZFNs. These companies include 2seventy bio, Allogene Therapeutics, Cellectis, Precision BioSciences and Sangamo Therapeutics.

We are also aware of companies developing therapies in various areas related to our specific research and development programs. In hemoglobinopathies, these companies include Beam Therapeutics, bluebird bio, Editas Medicine, Graphite Bio, Merck Sharp & Dohme, Novartis Pharmaceuticals, Pfizer, and Sangamo Therapeutics. In immuno-oncology, these companies include 2seventy bio, Adicet Bio, Allogene Therapeutics, Bristol Myers Squibb, Caribou Biosciences, Cellectis, Century Therapeutics, Fate Therapeutics, Gilead Sciences, Legend Biotech, Novartis Pharmaceuticals, Poseida Therapeutics and Precision BioSciences. In

regenerative medicine, these companies include BlueRock Therapeutics (acquired by Bayer in 2019), Sana Biotechnology and Semma Therapeutics (acquired by Vertex in 2019). In *in vivo*, these companies include Alnylam Pharmaceuticals, Arrowhead Pharmaceuticals, BioMarin Pharmaceutical, Intellia Therapeutics, Ionis Pharmaceuticals and Verve Therapeutics.

Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications and there can be no certainty that other gene editing technologies will not be considered better or more attractive than our technology for the development of products. For example, Cas9 may be determined to be less attractive than other CRISPR proteins, such as Cas12a or novel Cas enzymes that have yet to be discovered, or other CRISPR-associated nuclease variants that can edit human DNA, such as base editors and prime editors.

In addition to competition from other gene editing therapies or gene or cell therapies, any product we may develop may also face competition from other types of therapies, such as small molecule, antibody or protein therapies. In addition, new scientific discoveries may cause CRISPR/Cas9 technology, or gene editing as a whole, to be considered an inferior form of therapy.

In addition, many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene and cell 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. 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, have broader acceptance and higher rates of reimbursement by third-party payors or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, convenience, and availability of reimbursement.

If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene editing, gene therapy, and cell therapy products. Competition with other related products currently under development may include competition for clinical trial sites, patient recruitment, and product sales. In addition, due to the intense research and development taking place in the gene editing field, including by us and our competitors, the intellectual property landscape is in flux and highly competitive. There may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third-party, intellectual property and proprietary rights in the future. For example, see our discussion of the ‘048 interference, the ‘115 interference and European opposition proceedings in “*Risks Related to Intellectual Property—Third-party Claims Of Intellectual Property Infringement Against Us, Our Licensors Or Our Collaborators May Prevent Or Delay Our Product Discovery and Development Efforts.*”

Moreover, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors’ products and our patents may not be sufficient to prevent our competitors from commercializing competing products. The availability of our competitors’ products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

Even If We Are Able To Commercialize Any Product Candidates, Such Products May Become Subject To Unfavorable Pricing Regulations, Third-party Reimbursement Practices, Or Healthcare Reform Initiatives, Which Would Harm Our Business.

The regulations that govern marketing approvals, pricing, and reimbursement for new biologic products vary widely from country to country. Some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Third-party payors, such as private health insurers, health maintenance organizations, and governmental programs such

as Medicare and Medicaid, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Governmental and private third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product that we commercialize and, if reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval. See the sections entitled "*Business—Coverage, Pricing and Reimbursement*" and "*Business—Healthcare Reform*."

There may be significant delays in obtaining reimbursement for newly approved products, and reimbursement coverage may be more limited than the purposes for which the product is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the product and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost products and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of products from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved products we may develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

Risks Related to Our Relationships with Third Parties

Our Collaborators And Strategic Partners May Control Aspects Of Our Clinical Trials and Commercialization Efforts, Which Could Result In Delays And Other Obstacles In The Commercialization Of Our Proposed Products And Materially Harm Our Results Of Operations.

We have entered into strategic collaborations and licenses, including, for example, with Vertex and ViaCyte (which was acquired by Vertex in 2022), and may enter into additional collaborations and licenses with other third parties in the future. For some programs, we also depend on, or may in the future depend on, third-party collaborators and strategic partners to design and conduct our clinical trials, and for any approved products, the commercialization of such products. Some of these collaborations provide us with important technologies in order to more fully develop our product candidates and we may enter into collaborations with other companies to provide us with important technologies or funding for our programs. The success of these arrangements will depend heavily on the efforts and activities of our collaborators and licensing partners.

Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations and collaborators may not perform their obligations as expected. In some situations, we may not be able to influence our collaboration partners' decisions regarding the development and commercialization of our partnered product candidates, and as a result, our collaboration partners may not pursue or prioritize the development and commercialization of those partnered product candidates in a manner that is in our best interest. In addition, collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement or result in litigation or arbitration, which would be time-consuming and expensive. Collaborators may also fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product. Licensors generally have sole discretion in determining the efforts and resources that they will apply to the licensed products.

As a result, we may not be able to conduct any of our partnered programs in the manner or on the time schedule we currently contemplate, which may negatively impact our business operations. In addition, if any of these collaborators or strategic partners withdraw support for our programs or proposed products or otherwise impair their development or commercialization, our business could be negatively affected. Additionally, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

We Have Partnered With Vertex On Our Lead Program Exa-cel; Vertex Has Significant Control Over The Exa-cel Program.

We have entered into a series of agreements with Vertex that contemplate certain research, development, manufacturing and commercialization activities involving various targets. Pursuant to these agreements, Vertex has sole authority to conduct certain activities. For example, under our 2015 Collaboration Agreement with Vertex to research, develop and commercialize new treatments aimed at the underlying genetic causes of human diseases, Vertex had sole authority to select genetic targets to pursue and we do not have control over the development of any product candidates for the selected genetic targets. In addition, under our 2019 Collaboration Agreement with Vertex, Vertex has sole authority to develop and commercialize products for the treatment of DMD and DM1 under the agreement (subject to our option to co-develop and co-commercialize products for the treatment of DM1). In addition, in the third quarter of 2022, Vertex announced it had acquired ViaCyte, pursuant to which it will have joint rights to develop and commercialize product candidates and shared products for use in the treatment of diabetes type 1, diabetes type 2 and insulin dependent/requiring diabetes throughout the world.

Additionally, we are developing and preparing to commercialize exa-cel for TDT and SCD in partnership with Vertex under the A&R Vertex JDCA. Under the A&R Vertex JDCA, subject to the terms and conditions of such agreement, Vertex has the right to conduct all research, development, manufacturing and commercialization activities relating to the specified product candidates and products (including exa-cel) throughout the world subject to our reserved right to conduct certain activities. While we will continue to participate in certain aspects of such activities in an observer capacity unless and to the extent otherwise agreed to by the parties, and we and Vertex have an equal number of representatives on the joint oversight committee and transition committee, Vertex controls the development of exa-cel or any future product candidates subject to the A&R Vertex JDCA.

Our lack of control over the clinical development, manufacturing, regulatory submission and commercialization activities in certain of our agreements with Vertex could cause delays or other difficulties in the development and commercialization of product candidates, which may prevent among other things, completion of intended IND filings in a timely fashion, if at all, or the completion or delay in BLA filings. For example, there is no assurance that data obtained from our partnered exa-cel programs will indicate clinically meaningful benefit or support approval of a BLA, and we cannot be certain that data from CLIMB-111 and CLIMB-121 clinical trials will be sufficiently robust from a safety and/or efficacy perspective to support either conditional approval or full approval. The FDA may require that we and Vertex conduct additional or larger pivotal trials before we and Vertex can complete our rolling submission or obtain approval of a BLA. Furthermore, we are required to submit data relating to certain release assays designed to confirm the quality, purity and strength (including potency) of exa-cel as a condition for completing the BLA submission. Under the A&R Vertex JDCA, Vertex is responsible for such clinical trials and manufacturing. If Vertex is unable to submit the required data in a timely manner, there is the potential for further delaying the completion of our BLA submission, with the potential consequence of delaying any approval and commercial launch of exa-cel in the United States.

In addition, the termination of our agreements with Vertex would prevent us from receiving any milestone, royalty payments and other benefits under that agreement, which may have a materially adverse effect on our results of operations.

If Conflicts Arise Between Us And Our Collaborators Or Strategic Partners, These Parties May Act In A Manner Adverse To Us And Could Limit Our Ability To Implement Our Strategies.

If conflicts arise between our corporate or academic collaborators or strategic partners and us, the other party may act in a manner adverse to us and could limit our ability to implement our strategies. Some of our academic collaborators and strategic partners are conducting multiple product development efforts within each area that is the subject of the collaboration with us. Our collaborators or strategic partners, however, may develop, either alone or with others, products in related fields that are competitive with the products or potential products that are the subject of these collaborations. For example, Vertex may prioritize its solely owned diabetes program to the detriment of the diabetes program we have with ViaCyte (which was acquired by Vertex in 2022). Competing products, either developed by the collaborators or strategic partners or to which the collaborators or strategic partners have rights, may result in the withdrawal of partner support for our product candidates.

Current or future collaborators or strategic partners could also become our competitors in the future. Our collaborators or strategic partners could develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, or fail to devote sufficient resources to the development and commercialization of products. Any of these developments could harm our product development efforts.

Our Collaborators Or Strategic Partners May Decide To Adopt Alternative Technologies Or May Be Unable To Develop Commercially Viable Products With Our Technology, Which Would Negatively Impact Our Revenues And Our Strategy To Develop These Products.

Our collaborators or strategic partners may adopt alternative technologies, which could decrease the marketability of our CRISPR/Cas9 gene editing technology. For example, Vertex is also advancing other therapeutic product candidates targeting diabetes. Additionally, because our current collaborators or strategic partners are and we anticipate that any future collaborators or strategic partners will be working on more than one development project, they could choose to shift their resources to projects other than those

they are working on with us. If they do so, this would delay our ability to test our technology and would delay or terminate the development of potential products based on our CRISPR/Cas9 gene editing technology. Further, our collaborators and strategic partners may elect not to develop products arising out of our collaborative and strategic partnering arrangements or to devote sufficient resources to the development, manufacturing, marketing or sale of these products. The failure to develop and commercialize a product candidate pursuant to our agreements with our current or future collaborators would prevent us from receiving future milestone and royalty payments which would negatively impact our revenues.

We May Seek To Establish Additional Collaborations And, If We Are Not Able To Establish Them On Commercially Reasonable Terms, We May Have To Alter Our Development And Commercialization Plans.

Our product candidate development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with additional pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for any additional collaborations will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, we have granted exclusive rights to Vertex for certain genetic targets, and during the term of the collaboration agreements, we will be restricted from granting rights to other parties to use our gene editing technology to pursue therapies that address these genetic targets. The non-competition provisions in this agreement could limit our ability to enter into strategic collaborations with future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If we are unable to negotiate and enter into new collaborations, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

We Expect To Rely On Third Parties To Conduct Our Clinical Trials And Certain Aspects Of Our Preclinical Studies For Our Product Candidates. If These Third Parties Do Not Successfully Carry Out Their Contractual Duties, Comply With Regulatory Requirements Or Meet Expected Deadlines, We May Not Be Able To Obtain Regulatory Approval For Or Commercialize Our Product Candidates And Our Business Could Be Substantially Harmed.

We expect to rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct future clinical trials and we currently rely on third parties to conduct certain aspects of our preclinical studies for our product candidates. Nevertheless, we are responsible for ensuring that each of our preclinical studies and any future clinical trials we sponsor are conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards and our reliance on CROs will not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulations, commonly referred to as Good Clinical Practices, or 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. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions. For any violations of laws and regulations during the conduct of our preclinical studies and clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

We and our CROs will be required to comply with regulations, including GCPs, for conducting, monitoring, recording and reporting the results of preclinical studies and clinical trials to ensure that the data and results are scientifically credible and accurate and that the trial patients are adequately informed, among other things, of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable health regulatory authorities for any drugs in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and FDA or comparable health regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our future clinical trials will comply with GCPs. In addition, our future clinical trials must be conducted with product candidates produced in accordance with the requirements in cGMP regulations. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action and require significantly greater expenditures.

Although we intend to design the clinical trials for our product candidates, CROs will conduct all of the clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future preclinical studies and clinical trials will also result in less direct control over the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our preclinical studies and clinical trials and may subject us to unexpected cost increases that are beyond our control. If the CROs do not perform preclinical studies and future clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development, regulatory approval and commercialization of our product candidates may be delayed, we may not be able to obtain regulatory approval and commercialize our product candidates, or our development programs may be materially and irreversibly harmed. If we are unable to rely on preclinical and clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of any clinical trials we conduct and this could significantly delay commercialization and require significantly greater expenditures.

Our Relationships With Healthcare Providers, Physicians, And Third-party Payors Will Be Subject To Applicable Anti-kickback, Fraud And Abuse And Other Healthcare Laws And Regulations, Which Could Expose Us To Criminal Sanctions, Civil Penalties, Exclusion From Government Healthcare Programs, Contractual Damages, Reputational Harm And Diminished Profits And Future Earnings.

Although we do not currently have any products on the market, once we begin commercializing our product candidates, if ever, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the U.S. federal government and states as well as other national, regional or local governments in other jurisdictions in which we conduct our business.

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates that we may develop for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell, and distribute our product candidates for which we obtain marketing approval. See the section entitled "*Business—Healthcare Law and Regulation*."

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products is prohibited in the EU. The provision of benefits or advantages to induce or reward improper performance generally is also governed by the national anti-bribery laws of EU Member States, and the Bribery Act 2010 in the UK. Infringement of these laws could result in substantial fines and imprisonment. EU Directive 2001/83/EC, which is the EU Directive governing medicinal products for human use, further provides that, where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy. This provision has been transposed into the Human Medicines Regulations 2012 and so remains applicable in the UK despite its departure from the EU.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization, and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, or case law involving applicable fraud and abuse or other healthcare laws and regulations. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations, including activities that may be conducted by sales and marketing team we establish, 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, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Risks Related to Manufacturing

Gene Editing Products Are Novel And May Be Complex And Difficult To Manufacture. We Could Experience Manufacturing Problems That Result In Delays In The Development Or Commercialization Of Our Product Candidates Or Otherwise Harm Our Business.

The manufacturing process used to produce CRISPR/Cas9-based product candidates may be complex, as they are novel and have not been validated for clinical and commercial production. Several factors could cause production interruptions, including inability to develop novel manufacturing processes, equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, including the coronavirus pandemic, disruption in utility services, human error or disruptions in the operations of our suppliers, including acquisition of the supplier by a third party or declaration of bankruptcy. The expertise required to manufacture these product candidates may be unique to a particular contract manufacturing organizations, and as a result, it would be difficult and time consuming to find an alternative contract manufacturing organization. Failure or process defects in any of the interrelated systems at either our manufacturing facility, once validated, or those of our third-party manufacturers, could adversely impact our ability to manufacture and supply cell therapy product candidates and certain components thereof intended for research, clinical and, if approved, commercial production. For additional information regarding the impact of the coronavirus pandemic, please see "*Our Business May Be Adversely Affected By The Ongoing Coronavirus Pandemic, Including the Emergence of Additional Variants*."

Our product candidates will require processing steps that are more complex than those required for most small molecule drugs. Moreover, unlike small molecules, the physical and chemical properties of biologics generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we will employ multiple steps to control the manufacturing process to assure that the process works and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical grade materials that meet FDA, the EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA, the EMA and other health regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, the EMA or other health regulatory authorities may require that we not distribute a lot until the relevant agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. Lot failures could cause us to delay product launches or clinical trials and we may need to conduct product recalls, all of which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. Problems in our manufacturing process could restrict our ability to meet market demand for our products.

We also may encounter problems hiring and retaining directly or through contract manufacturing organizations the experienced scientific, quality assurance, quality control and manufacturing personnel needed to operate our manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements. Any problems in our supply chain, manufacturing process or facilities could result in delays in planned clinical trials and increased costs, and could make

us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in our manufacturing process could restrict our ability to meet potential future market demand for products.

The Manufacturing Facilities For Our Product Candidates Are Subject To Rigorous Regulations And Failure To Obtain Or Maintain Regulatory Approvals Or Operate In Line With Established cGMPs And International Best Practices Could Delay Or Impair Our Ability To Commercialize Our Product Candidates.

We and the third-party manufacturers of our product candidates are subject to applicable cGMPs prescribed by the FDA and other rules and regulations prescribed by the EMA and other regulatory authorities. To obtain FDA and EMA approval for our product candidates in the United States and Europe, we need to undergo strict pre-approval inspections of our or our third-party manufacturing facilities. When inspecting our or our contractors' manufacturing facilities, the FDA or EMA might cite cGMP deficiencies, both minor and significant, which we may not be required to disclose. Remediating deficiencies can be laborious and costly and consume significant periods of time. Moreover, if the FDA or EMA notes deficiencies as a result of its inspection, it will generally reinspect the facility to determine if the deficiency has been remediated to its satisfaction. The FDA or EMA may note further deficiencies as a result of its reinspection, either related to the previously identified deficiency or otherwise. If we or the manufacturers of our product candidates cannot satisfy the FDA and EMA as to compliance with cGMP in a timely basis, marketing approval for our product candidates could be seriously delayed, which in turn would delay commercialization of our product candidates.

We Are Subject To Regulatory And Operational Risks Associated With Our Internal Manufacturing Facility And At Those Of Our Third-party Contract Manufacturing Partners.

In the fourth quarter of 2021, we completed construction of a new cell therapy manufacturing facility in Framingham, Massachusetts, that, among other things, once validated, will be capable of supporting research, clinical and commercial production of our cell therapy product candidates and certain components thereof for certain of our programs. We are progressing the regulatory validation activities required to bring this facility into cGMP compliance and to enable us to produce cell therapy product supply suitable for human administration in the future. We have never before built and operated our own manufacturing facility, and we can provide no assurances that we will be able to build out and operate our internal manufacturing capacity or achieve required validation of our Framingham facility. While the design of the facility is based on current standards for biotechnology facilities, it has not yet been reviewed or pre-approved by any regulatory agency, nor has the facility been inspected by any regulatory agency such as the FDA. We could incur delays in implementing the full operational state of the facility, causing delays to clinical supply or extended use of our third-party contract manufacturing partners, resulting in unplanned expenses. In constructing our facility in Framingham, Massachusetts, we have incurred substantial expenditures, and expect to incur significant additional expenditures in validating and operating the facility in the future.

We Expect To Rely On Third Parties To Manufacture Our Clinical Product Supplies, And We Intend To Rely On Third Parties For At Least A Portion Of The Manufacturing Process Of Our Product Candidates. Our Business Could Be Harmed If The Third Parties Experience Supply Chain Shortages, Fail To Provide Us With Sufficient Quantities Of Product Inputs Or Fail To Do So At Acceptable Quality Levels Or Prices.

Although we have completed construction of our facility in Framingham, Massachusetts, we have not yet completed regulatory validation activities and we do not own any facility that currently may be used as our clinical-scale manufacturing and processing facility and must rely on outside vendors to manufacture supplies and process our product candidates in connection with any clinical trial we undertake of such product candidates. We have not yet caused any product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. We will make changes as we work to optimize the manufacturing process, and we cannot be sure that even minor changes in the process will result in therapies that are safe and effective.

The facilities used to manufacture our product candidates must be evaluated by the FDA, or other health regulatory agencies in other jurisdictions, pursuant to inspections that will be conducted after we submit an application to the FDA or other health regulatory agencies. We will not control the manufacturing process of, and will be completely dependent on, our contract manufacturing partners for compliance with regulatory requirements, known as cGMP requirements, for manufacture of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities or regulatory authorities may cite them for deficiencies, and we may not be able to obtain or may be delayed in obtaining regulatory approval from the FDA or other regulatory authorities for our product candidates. In addition, we have no direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable health regulatory authority does not approve these facilities or cites these facilities for deficiencies for the manufacture of our product candidates or if it withdraws any such approval or cites deficiencies in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. In addition, if our contract manufacturers are unable to timely perform or

become distracted as a result of actions taken by the FDA or a comparable health regulatory authority or as a result of the coronavirus pandemic, we may experience manufacturing delays or may need to find alternative manufacturing facilities, which in each case, would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

Our reliance on a limited number of third-party manufacturers exposes us to a number of risks, including the following:

- we may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited;
- a new manufacturer would have to be educated in, or develop substantially equivalent processes for, the production of our product candidates;
- a change in manufacturers or certain changes in manufacturing processes/procedures will require that we conduct a manufacturing comparability study to verify that any new manufacturer or manufacturing process/procedures will produce our product candidate according to the specifications previously submitted to the FDA or other regulatory authority, and such study may be unsuccessful;
- our third-party manufacturers might be unable to timely manufacture our product candidates or produce the quantity and quality required to meet our clinical and commercial needs, if any;
- contract manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately;
- our contract manufacturers may not perform as agreed, may not devote sufficient resources to our product candidates or may not remain in the contract manufacturing business for the time required to supply our clinical trials;
- manufacturers are subject to ongoing periodic unannounced inspection by the FDA and corresponding state agencies to ensure strict compliance with cGMP and other government regulations and corresponding foreign standards and we have no control over third-party manufacturers' compliance with these regulations and standards;
- we may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our product candidates;
- our third-party manufacturers could breach or terminate their agreements with us;
- raw materials and components used in the manufacturing process, particularly those for which we have no other source or supplier, may not be available or may not be suitable or acceptable for use due to material or component defects;
- our contract manufacturers and critical reagent suppliers may be subject to inclement weather, as well as natural or man-made disasters; and
- our contract manufacturers may have unacceptable or inconsistent product quality success rates and yields, and we have no direct control over our contract manufacturers' ability to maintain adequate quality control, quality assurance and qualified personnel.

Each of these risks could delay or prevent the completion of our clinical trials or the approval of any of our product candidates by the FDA, result in higher costs or adversely impact commercialization of our product candidates, if approved. In addition, we will rely on third parties to perform certain specification tests on our product candidates prior to delivery to patients. If these tests are not appropriately done and test data are not reliable, patients could be put at risk of serious harm and the FDA could place significant restrictions on our company until deficiencies are remedied.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

Our Future Success Depends On Our Ability To Retain Key Executives And To Attract, Retain And Motivate Qualified Personnel.

We are highly dependent on the research and development, clinical, commercial and business development expertise of Dr. Samarth Kulkarni, our Chief Executive Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. The loss of the services of our executive officers or other key employees or consultants could impede the achievement of our research, development

and commercialization objectives and seriously harm our ability to successfully implement our business strategy. If we are unable to retain high quality personnel, our ability to pursue our growth strategy will be limited.

We will also need to recruit and retain qualified scientific, clinical and commercial personnel as we advance the development of our product candidates and product pipeline. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific, clinical and commercial personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

Swiss Corporate Governance With Respect To Executive Compensation May Affect Our Business.

Swiss corporate law, among other things, (a) requires a binding shareholder "say on pay" vote with respect to the compensation of members of our executive management and board of directors, (b) generally prohibits the making of severance, advance, transaction premiums and similar payments to members of our executive management and board of directors and (c) requires companies to specify various compensation-related matters in their articles of association, thus requiring them to be approved by a shareholders' vote. At our annual general meetings, our shareholders are required to approve the maximum aggregate compensation of our board of directors and our executive management team. Swiss law further provides for criminal penalties against directors and members of executive management in case of non-compliance with certain of the requirements regarding compensation. Such provisions may negatively affect our ability to attract and retain executive management and members of our board of directors.

Our Employees, Principal Investigators, Consultants And Commercial Partners May Engage In Misconduct Or Other Improper Activities, Including Non-compliance With Regulatory Standards And Requirements And Insider Trading.

We are exposed to the risk of fraud or other misconduct by our employees, consultants, commercial partners, and principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions, provide accurate information to the FDA, the European Commission, and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and in other jurisdictions, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations, and prospects, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

If We Fail To Comply With Environmental, Health And Safety Laws And Regulations, We Could Become Subject To Fines Or Penalties Or Incur Costs That Could Harm Our Business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes. We will not be able to eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from any use by us of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Product Liability Lawsuits Against Us Could Cause Us To Incur Substantial Liabilities And Could Limit Commercialization Of Any Product Candidates That We May Develop.

We will face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any product candidates that we may develop. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any product candidates that we may develop.

Although we have obtained product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. Further, we anticipate that we will need to increase our insurance coverage if we successfully commercialize any product candidate. 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.

If We Fail To Establish And Maintain Proper And Effective Internal Control Over Financial Reporting, Our Operating Results And Our Ability To Operate Our Business Could Be Harmed.

Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. We are required to comply with the requirements of The Sarbanes-Oxley Act of 2002, or SOX, which requires that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation, document our controls and perform testing of our key control over financial reporting to allow management and our independent public accounting firm to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of SOX. Our testing, or the subsequent testing by our independent public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses. If we are not able to comply with the requirements of Section 404 in a timely manner, or if we or our accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock would likely decline and we could be subject to lawsuits, sanctions or investigations by regulatory authorities, which would require additional financial and management resources.

We continue to invest in more robust technology and in more resources in order to manage those reporting requirements. Implementing the appropriate changes to our internal controls may distract our officers and employees, result in substantial costs if we implement new processes or modify our existing processes and require significant time to complete. Any difficulties or delays in implementing these controls could impact our ability to timely report our financial results. In addition, we currently rely on a manual process in some areas which increases our exposure to human error or intervention in reporting our financial results. For these reasons, we may encounter difficulties in the timely and accurate reporting of our financial results, which would impact our ability to provide our investors with information in a timely manner. As a result, our investors could lose confidence in our reported financial information, and our stock price could decline.

In addition, any such changes do not guarantee that we will be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy could prevent us from accurately reporting our financial results.

We May Fail To Comply With Evolving European And Other Privacy Laws.

We currently conduct clinical trials in the EEA. As a result, we are subject to additional privacy laws. The GDPR became effective on May 25, 2018, and deals with the processing of personal data and on the free movement of such data. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, including requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside the EEA, including to the United States, providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR increases substantially the penalties to which we could be subject in the event of any non-compliance, including fines of up to €10,000,000 or up to 2% of our total worldwide annual turnover for certain comparatively minor offenses, or up to €20,000,000 or up to 4% of our total worldwide annual turnover for more serious offenses.

In particular, national laws of Member States of the EU have implemented national laws which may partially deviate from the GDPR and impose different and more restrictive obligations from country to country, so that we do not expect to operate in a uniform legal landscape in the EU. Also, as it relates to processing and transfer of genetic data, the GDPR specifically allows EU Member State nations to enact laws that impose additional and more specific requirements or restrictions, and European laws have historically differed quite substantially in this field, leading to additional uncertainty.

In addition, further to the UK's exit from the EU on January 31, 2020, the GDPR ceased to apply in the UK at the end of the transition period on December 31, 2020. However, as of January 1, 2021, the UK's European Union (Withdrawal) Act 2018 incorporated the GDPR (as it existed on December 31, 2020 but subject to certain UK specific amendments) into UK law, referred to as the UK GDPR. The UK GDPR and the UK Data Protection Act 2018 set out the UK's data protection regime, which is independent from but aligned to the EU's data protection regime. The UK Government has announced plans to reform its data protection legal framework in its Data Reform Bill but those have been put on hold. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher. Although the UK is regarded as a third country under the EU's GDPR, the European Commission ("EC") has now issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing.

The EU-U.S. and the Swiss-U.S. Privacy Shield frameworks allowed U.S. companies that self-certify to the U.S. Department of Commerce and publicly commit to comply with specified requirements to import personal data from the EU and Switzerland. In 2020, the Court of Justice of the EU ruled that the EU-U.S. Privacy Shield is an invalid transfer mechanism, which was one of the primary mechanisms used by U.S. companies to import personal information from Europe in compliance with the GDPR's cross-border data transfer restrictions, and raised questions about whether the European Commission's Standard Contractual Clauses, or SCCs, one of the primary alternatives to the Privacy Shield, can lawfully be used for personal information transfers from Europe to the United States or most other countries. Similarly, the Swiss Federal Data Protection and Information Commissioner has opined that the Swiss-U.S. Privacy Shield is inadequate for transfers of data from Switzerland to the United States and the UK Information Commissioner's Office has stated that the Privacy Shield framework is inadequate for transfers from the UK to the United States. Furthermore, on June 4, 2021, the European Commission issued new forms of standard contractual clauses for data transfers from controllers or processors in the EEA (or otherwise subject to the GDPR) to controllers or processors established outside the EEA. The new forms of standard contractual clauses have replaced the standard contractual clauses that were adopted previously under the Data Protection Directive. We will be required to transition to the new forms of standard contractual clauses and doing so may require significant effort and cost. The new standard contractual clauses may also impact our business as companies based in Europe may be reluctant to utilize the new clauses to legitimize transfers of personal information to third countries given the burdensome requirements of transfer impact assessments and the substantial obligations that the new standard contractual clauses impose upon exporters. On March 25, 2022, the European Commission and the United States announced to have reached a political agreement on a new "Trans-Atlantic Data Privacy Framework", which will replace the invalidated Privacy Shield and on December 13, 2022, the European Commission published a draft adequacy decision on the Trans-Atlantic Data Privacy Framework. If we are investigated by a European data protection authority, we may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on our existing business and on our ability to attract and retain new clients or pharmaceutical partners. We may also experience hesitancy, reluctance, or refusal by European or multi-national clients or pharmaceutical partners to continue to use our products due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or pharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain, or otherwise objectionable and therefore decide not to do business with us. Any of the foregoing could materially harm our business, prospects, financial condition, and results of operations.

Our Business And Operations May Be Negatively Impacted By The United Kingdom's Withdrawal From The EU.

On June 23, 2016, the UK held a referendum in which a majority of the eligible members of the electorate voted to leave the EU, commonly referred to as Brexit. The UK formally left the EU on January 31, 2020, however there was an initial transition period until December 31, 2020 during which EU rules and legislation continued to apply. The UK and EU have signed a EU-UK Trade and Cooperation Agreement, or the TCA, which became provisionally applicable on January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of Good Manufacturing Practice, or GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore aligns in many ways with EU regulations, however it is possible that these regimes will more significantly diverge in the future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual

recognition of UK and EU pharmaceutical legislation. It remains to be seen how Brexit will impact regulatory requirements for medicinal products and devices in the UK in the long-term.

Since the expiry of the transition period, Great Britain is no longer covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland). For a period of three years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required. Any new divergent regulations in Great Britain and the EU could add time and expense to the conduct of our business, as well as the process by which our products receive regulatory approval in the UK, the EU and elsewhere. Any of these longer-term effects of Brexit, and others we cannot anticipate, could negatively impact our business and results of operations. Our UK operations support our current and future operations and clinical activities (including, without limitation, clinical activities for exa-cel) in other countries in the EU and European Economic Area, or EEA, and these operations and clinical activities could be disrupted by the longer term effects of Brexit.

Our Business Operations Have a Substantial International Footprint and We May Further Expand In The Future, Which Presents Challenges In Managing Our Business Operations.

We are headquartered in Zug, Switzerland and have offices in the United States and the United Kingdom. In addition, we may expand our international operations into other countries in the future. While we have acquired significant management and other personnel with substantial experience, conducting our business in multiple countries subjects us to a variety of risks and complexities that may materially and adversely affect our business, results of operations, financial condition and growth prospects, including, among other things:

- the increased complexity and costs inherent in managing international operations;
- diverse regulatory, financial and legal requirements, and any future changes to such requirements, in one or more countries where we are located or do business;
- country-specific tax, labor and employment laws and regulations;
- challenges inherent in efficiently managing employees in diverse geographies, including the need to adapt systems, policies, benefits and compliance programs to differing labor and other regulations;
- liabilities for activities of, or related to, our international operations or product candidates;
- changes in currency rates; and
- regulations relating to data security and the unauthorized use of, or access to, commercial and personal information.

We continue to expand our operations, and our corporate structure and tax structure is complex. In connection with our current and future potential partnerships, we are actively engaged in developing and applying technologies and intellectual property with a view toward commercialization of products globally, often with commercialization partners. In connection with those activities, we already have and will likely continue to engage in complex cross-border and global transactions involving our technology, intellectual property and other assets, between us and other entities such as partners and licensees, and between us and our subsidiaries. Such cross-border and global arrangements are both difficult to manage and can potentially give rise to complexities in areas such as tax treatment, particularly since we are subject to multiple tax regimes and different tax authorities can also take different views from each other, even as regards the same cross-border transaction or arrangement. There can be no assurance that we will effectively manage this increased complexity without experiencing operating inefficiencies, control deficiencies or tax liabilities. Significant management time and effort is required to effectively manage the increased complexity of our company, and our failure to successfully do so could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Risks Related to Intellectual Property

If We Are Unable To Obtain Or Protect Intellectual Property Rights Related to Our Proprietary Gene Editing Technology And Product Candidates, We May Not Be Able To Compete Effectively In Our Markets.

Our success depends in large part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other jurisdictions with respect to our CRISPR/Cas9 platform technology and any proprietary product candidates and technology we develop. We rely upon a combination of intellectual property rights, including patent rights, trade secret protection and confidentiality agreements to protect the intellectual property related to our gene editing technology and product candidates. Presently we have rights to certain intellectual property, through licenses from third parties and under patent rights that we own, to develop our gene editing technology and/or product candidates. For example, through our 2014 exclusive license with Dr. Charpentier, we exclusively license certain rights to a worldwide patent portfolio, including more than ninety-five (95) granted or

allowed patents, as well as pending patent applications, which covers various aspects of our gene editing platform technology, including, for example, compositions of matter (e.g., CRISPR/Cas9 systems), and methods of use, including the use of a CRISPR/Cas9 system for gene editing. We refer to this worldwide patent portfolio as the "Patent Portfolio". In addition, we have filed numerous patent applications covering our product candidates, which cover various aspects of our product candidates, including, for example, compositions of matter, as well as methods of making and using.

We seek to protect our proprietary position by in-licensing intellectual property to cover our platform technology and filing patent applications in the United States and in other jurisdictions related to our technologies and product candidates that are important to our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position. If we or our licensors are unable to obtain or maintain patent protection with respect to our CRISPR/Cas9 platform technology and any proprietary products and technology we develop, our business, financial condition, results of operations and prospects could be materially harmed.

However, the strength of patents in the biotechnology and pharmaceutical field generally, and the genome-editing field in particular, involves complex legal and scientific questions and can be uncertain and we cannot offer any assurances about which, if any, patent rights that we own or in-license will issue, the breadth of any such patent rights or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. For example, the scope of patent protection that will be available to us in the United States and in other countries is uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our intellectual property, obtain, maintain, defend and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and in-licensed patents. With respect to both in-licensed and owned intellectual property, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors, or if any such patents will be found invalid, unenforceable or not infringed if challenged by our competitors.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license 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 in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our gene editing technology and/or product candidates. It is possible that we have failed to identify relevant third-party patents or applications. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with any degree of certainty whether the inventors of our licensed patents and applications were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, there is no assurance that all of the potentially relevant prior art relating to our owned and in-licensed patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application.

The ultimate outcome of any pending or allowed patent application or granted patent is uncertain and the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we license or own currently in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage.

Additionally, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability and our owned and in-licensed patents may be challenged in the courts or patent offices in the United States and in other jurisdictions. There is a substantial amount of litigation as well as administrative proceedings for challenging patents, including interference, derivation, reexamination, and other post-grant proceedings before the USPTO and oppositions and other comparable proceedings in foreign jurisdictions, involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, and we expect this to be true for the CRISPR/Cas9 space as well. See "*Risk Factors —Risks Related to Intellectual Property—Third-party Claims Of Intellectual Property Infringement Against Us, Our Licensors Or Our Collaborators May Prevent Or Delay Our Product Discovery and Development Efforts"* for more information. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, revoked, invalidated or held unenforceable, in whole or in part, which could limit our ability to practice the invention or 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. 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 in-licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Competitors may also claim that they invented the inventions claimed in such issued patents or patent applications prior to our inventors, or may have filed patent applications before our inventors did. A competitor may also claim that our products and technology infringe its patents and that we therefore cannot practice our technology as claimed under our patent applications, if issued. An adverse determination in any such claim may result in our inability to manufacture or commercialize products without infringing third-party patent rights. Competitors may also contest our patents, if issued, by showing that the invention was not patent-eligible, was not novel, was obvious or that the patent claims failed any other requirement for patentability. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights or allow third parties to commercialize our technology or products and compete directly with us, without payment to us.

Moreover, we, or one of our licensors, may have to participate in additional interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a non-U.S. patent office, that challenge priority of invention or other features of patentability. Such challenges may result in loss of patent rights, loss of exclusivity or freedom to operate, or in patent claims being narrowed, revoked, 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 product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

Further, even if they are unchallenged, our owned and in-licensed patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. If the breadth or strength of protection provided by the patent applications we hold is threatened, this could dissuade companies from collaborating with us to develop, and could threaten our ability to commercialize, product candidates. Consequently, we do not know whether any of our genome-editing platform advances and product candidates will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. For example, we are aware that third parties have suggested the use of the CRISPR technology in conjunction with a protein other than Cas9. Our owned and in-licensed patents may not cover such technology. If our competitors commercialize the CRISPR technology in conjunction with a protein other than Cas9, our business, financial condition, results of operations, and prospects could be materially adversely affected. Further, if we encounter delays in our clinical trials, the period of time during which we could market product candidates under patent protection would be reduced.

Because our gene editing technology and product candidates could require the use of proprietary rights held by third parties, the growth of our business could depend in part on our ability to acquire, in-license, or use these proprietary rights. We may be unable to acquire or in-license such intellectual property rights from third parties that we identify. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. Furthermore, as industry, government, academia and other biotechnology and pharmaceutical research expands and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others. We cannot guarantee that our gene editing technology, product candidates or the use of such product candidates do not infringe third-party patents. Because patent rights are granted jurisdiction-by-jurisdiction, our freedom to practice certain technologies, including our ability to research, develop and commercialize our product candidates, may differ by country.

Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business. Our pending and future patent applications or the patent applications that we obtain rights to through in-licensing arrangements may not result in patents being issued which protect our technology or future product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or

independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business.

Third-party Claims Of Intellectual Property Infringement Against Us, Our Licensors Or Our Collaborators May Prevent Or Delay Our Product Discovery and Development Efforts.

Our commercial success depends in part on our avoiding infringement of the valid patents and proprietary rights of third parties.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. As industry, government, academia and other biotechnology and pharmaceutical research expands and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others. We cannot guarantee that our technology, future product candidates or the use of such product candidates do not infringe third-party patents. It is also possible that we have failed to identify relevant third-party patents or applications. Because patent rights are granted jurisdiction-by-jurisdiction, our freedom to practice certain technologies, including our ability to research, develop and commercialize our product candidates, may differ by country.

Third parties may assert that we infringe their patents or that we are otherwise employing their proprietary technology without authorization, and may sue us. There may be third-party patents of which we are currently unaware with claims to compositions, formulations, methods of manufacture or methods of use or treatment that cover product candidates we discover and develop. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies or the manufacture, use or sale of our product candidates infringes upon these patents. If any such third-party patents were held by a court of competent jurisdiction to cover our technologies or product candidates, the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business.

Third-party Claims Of Intellectual Property May Prevent Or Delay Our Product Discovery and Development Efforts.

Third parties may seek to claim intellectual property rights that encompass or overlap with intellectual property that we own or license from them or others. Legal proceedings may be initiated to determine the scope and ownership of these rights, and could result in our loss of rights, including injunctions or other equitable relief that could effectively block our ability to further develop and commercialize our product candidates. Interference or derivation proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to, or the correct inventorship of, our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation, interference or derivation proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees.

For example, third parties could assert that we do not have rights to certain CRISPR/Cas9 technologies, or could assert and have asserted in the past, that the CVC Group does not have rights to certain CRISPR/Cas9 technologies, including inventorship and ownership rights to some of the CVC Group's patents, or that such rights are limited.

Specifically, the Broad Institute and Massachusetts Institute of Technology and, in some instances, the President and Fellows of Harvard College, which we refer to individually and collectively as the "Broad" owns a patent family that includes issued patents in the United States and Europe that claim certain aspects of CRISPR/Cas9 systems to edit DNA in eukaryotic cells, including human cells. In January 2016, the USPTO declared an interference (Interference No. 106,048, or '048 interference) between one of the then pending U.S. patent applications (now issued as U.S. Patent No. 10,266,850) included in the Patent Portfolio and twelve issued U.S.

patents owned jointly by the Broad to determine which set of inventors invented first and, thus, is entitled to patents on the invention in the United States. The PTAB concluded that the declared interference should be discontinued because the involved claim sets were considered patentably distinct from each other. Following appeal by the CVC Group, on September 10, 2018, the Federal Circuit affirmed the PTAB's decision to terminate the interference proceeding without determining which inventors actually invented the use of the CRISPR/Cas9 genome editing technology in eukaryotic cells.

Further, in June 2019, the USPTO declared a second interference (Interference No. 106,115, or '115 interference) between fourteen (14) pending U.S. patent applications co-owned by the CVC Group and thirteen (13) patents and a patent application co-owned by the Broad. The Broad patents include those that were the subject of the '048 interference. In September 2020, the PTAB issued an order that, among other matters, advanced the proceeding to the priority phase. In February 2022, PTAB issued a Decision of Priority and Judgment finding that Broad has priority over CVC Group with respect to the subject matter of the interference. The CVC Group has appealed this decision to the Federal Circuit. Any final decision by the Federal Circuit can be further appealed to the Supreme Court.

In addition to the Broad, other third parties, such as Vilnius University, ToolGen, Inc., MilliporeSigma (a subsidiary of Merck KGaA and formerly known as "Sigma-Aldrich") and Harvard University, filed patent applications claiming CRISPR/Cas9-related inventions around or within a year after the CVC Group application was filed and allege (or may allege) that they invented one or more of the inventions claimed by the CVC Group before the CVC Group. If the USPTO deems the scope of the claims of one or more of these parties to sufficiently overlap with the allowable claims from the CVC Group application, the USPTO could declare other interference proceedings to determine the actual inventor of such claims. For example, in December 2020, the USPTO declared an interference (Interference No. 106,127, or '127 interference) between a ToolGen patent application that claims certain aspects of CRISPR/Cas9 systems to edit DNA in eukaryotic cells, including human cells, and the same fourteen pending U.S. patent applications co-owned by the CVC Group that are involved in the '115 interference. This interference has been stayed pending a decision by the Federal Circuit in the '115 interference. The PTAB's judgment may be appealed to the Federal Circuit, and thru to the Supreme Court. In addition, in June 2021, the USPTO declared an interference (Interference No. 106,132, or '132 interference) between a MilliporeSigma patent application that claims certain aspects of CRISPR/Cas9 systems to edit DNA in eukaryotic cells, including human cells, and the same fourteen pending U.S. patent applications co-owned by the CVC Group that are involved in the '115 interference. This interference has been stayed pending a decision by the Federal Circuit in the '115 interference. Ultimately, the PTAB's judgment may be appealed to the Federal Circuit, and thru to the Supreme Court.

Each of the CVC Group, the Broad, ToolGen, Vilnius University, MilliporeSigma and Harvard University can pursue existing or new patent applications in the United States and elsewhere. Because the CVC Group and these other third parties all allege owning intellectual property claiming overlapping aspects of CRISPR/Cas9 systems and methods to edit DNA in eukaryotic cells, including human cells, our ability to market and sell CRISPR/Cas9-based human therapeutics may be adversely impacted depending on the scope and actual ownership over the inventions claimed in the competing patent portfolios.

Going forward, the USPTO could declare new interferences with the CVC Group, or us individually, related to the uses of the CRISPR/Cas9 technologies. Furthermore, we and the CVC Group continue to prosecute other patent claims covering the CRISPR/Cas9 inventions, which could also result in allowable or issued patents in the United States. Certain of the claims being prosecuted by the CVC Group and us, if found allowable by the USPTO, could lead to interference proceedings against patents or patent applications owned by third parties, including those listed above. If the USPTO deems the scope of the claims of one or more of these parties to sufficiently overlap with the allowable claims from a patent or patent application within the Patent Portfolio or our portfolio of patents, the USPTO could declare other interference proceedings to determine the first inventor of such claims. We cannot be certain which of these results, if any, will actually occur. If there are additional interferences, either party to the interference could again appeal an adverse decision to the Federal Circuit. Additionally, any of the CVC Group's existing or new patents or our existing or new patents could be the subject of other challenges to their validity or enforceability. The effects that any such results may have on us and our intellectual property position are currently unknown.

If any third party were to succeed in its interference and prevail in their inventorship claims or obtain patent claims that cover our product candidates or related activities through these various legal proceedings, such party could seek to assert its issued patents against us based on our CRISPR/Cas9-based activities, including commercialization. Third parties asserting their patent rights against us may seek and obtain injunctive or other equitable relief, which could effectively limit or block our ability to further develop and commercialize our product candidates. If we are found to infringe a third party's valid intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology, or avoid or invalidate such third party's intellectual property. These third parties would be under no obligation to grant to us any such license and such licenses may not be available on commercially reasonable terms or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we and our partners may need to cease the practice of our core gene editing, and the development, manufacture, and commercialization of one or more of the product candidates we may develop. 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 one or more of our product candidates, force us to redesign our infringing products or force us to cease some or all of our business operations, any of which could materially harm our business and could

prevent us from further developing and commercializing our proposed future product candidates thereby causing us significant harm. The loss of exclusivity or the narrowing of our patent claims could limit our ability to stop others from using or commercializing similar or identical technology and products. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Any of the foregoing could result in a material adverse effect on our business, financial condition, results of operations, or prospects. Defense of these claims, regardless of their merit, would involve substantial litigation expense, would be a substantial diversion of management and other employee resources from our business and may impact our reputation.

In any case, it may be years before there is a final determination on priority. Pursuant to the terms of the license agreement with Dr. Charpentier, we are responsible for covering or reimbursing Dr. Charpentier's patent prosecution, defense and related costs associated with our in-licensed technology.

Third-party owned IP relating to CRISPR/Cas9 or other related technologies necessary to develop, manufacture and commercialize viable CRISPR/Cas9 therapeutics – such as compositions of the products or components, methods of treatment, delivery technologies, chemical modifications, and analytical and manufacturing methods – could adversely impact our ability to ultimately market and sell products. Third parties may own intellectual property, including patents, that cover all or aspects of our technologies and potential products, and may be necessary for us to develop or commercialize viable products. If we are unable to successfully license, avoid or challenge such third-party intellectual property, we may not be able to develop and commercialize viable products in all or certain jurisdictions. In addition, if the intellectual property covering our products or technologies that we own or license were to be legally impaired or lost, we may be unable to realize sufficient financial returns to support the development or commercialization of our products.

Further, third parties routinely file international counterparts of their U.S. applications, some of which have been granted or could in the future be granted in Europe and/or other non-U.S. jurisdictions. We, as well as other parties have initiated opposition proceedings against some of these grants, and we may in the future oppose other grants to these or other applicants. Similarly, our intellectual property is and may in the future become involved in opposition proceedings in Europe or other jurisdictions. These oppositions could lead to the revocation of the patents in whole or in part, or could lead to the claims being narrowed in a way that could impair or preclude our ability to enforce the patents against competitors in Europe. For example, in February 2018, several parties filed oppositions in the European Patent Office to the grant of our first in-licensed European patent. Later in 2018 and in 2019, several parties filed oppositions in the European Patent Office to the grant of both our second and third in-licensed European patents. Opposition proceedings can lead to the revocation of a patent in its entirety; the maintenance of the patent as granted, or the maintenance of a patent in amended form. Opposition proceedings typically take years to resolve, including the time taken by appeals that can be filed by any of the parties. We cannot guarantee the outcome of the oppositions to our in-licensed European patent, and an adverse result could preclude us from enforcing our rights in Europe against third parties. For example, in early 2020, the European Patent Office upheld our first in-licensed European patent in amended form; in late 2021, they revoked our second European patent, and the decision is pending appeal.

We are unable to predict the outcome of these matters and are unable to make a meaningful estimate of the amount or range of loss, if any, that could result from an unfavorable outcome. In the future, we may become party to legal matters and claims arising in the ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

Our Rights To Develop And Commercialize Our Technology And Product Candidates Are Subject, In Part, To The Terms And Conditions Of Licenses Granted To Us By Others.

We are reliant upon licenses to certain intellectual property from third parties that are important or necessary to the development of our gene editing technology and product candidates. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use or cover all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses.

Moreover, under our in-license agreements, including our 2014 exclusive license agreement with Dr. Charpentier, we will be required to pay royalties based on our revenues from sales of our products utilizing the licensed technologies and these royalty payments could adversely affect the overall profitability for us of any products that we may seek to commercialize. Under each of our in-license agreements with Dr. Charpentier, we have an obligation to use commercially reasonable efforts to develop and obtain regulatory approval to market a licensed therapeutic product. Our in-license agreements with Dr. Charpentier also include an obligation to file an IND (or its equivalent in a major market country) by April 2021 and an obligation to file an IND (or its equivalent in a major market country) by April 2024. While we met the obligation to file an IND by April 2021, we may not be successful in meeting other remaining obligations in the future on a timely basis or at all. Our failure to meet the remaining obligations may give Dr. Charpentier the right to terminate our license rights. We will need to outsource and rely on third parties for many aspects of the clinical development of the products covered under our license agreements. Delay or failure by these third parties could adversely affect our ability to meet our diligence obligations and the continuation of our license agreements with third-party licensors.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. In addition, we may seek to obtain additional licenses from our licensors and, in connection with obtaining such licenses, we may agree to amend our existing licenses in a manner that may be more favorable to the licensors, including by agreeing to terms that could enable third parties (potentially including our competitors) to receive licenses to a portion of the intellectual property that is subject to our existing licenses. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

The Intellectual Property That Protects Our Core Gene Editing Technology Is Jointly Owned, And Our License Is From Only One Of The Joint Owners, Materially Limiting Our Rights In The United States And In Other Jurisdictions.

The Patent Portfolio we have exclusively licensed from Dr. Charpentier is the core patent protection for our gene editing technology. However, that family includes other named inventors who assigned their rights either to California or Vienna. As such, the Patent Portfolio is currently co-owned by Dr. Charpentier, California, and Vienna. On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement, or IMA, with California, Vienna and their licensees including Caribou and Caribou's licensee Intellia Therapeutics. Under the IMA, the co-owners provided reciprocal worldwide cross-consents to each of the other co-owners' licensees and sublicensees, and agreed to a number of other commitments and obligations with respect to supporting and managing the underlying CRISPR/Cas9 gene editing intellectual property, including a cost-sharing agreement. As explained more fully below, that leaves us in a position of holding only non-exclusive or co-exclusive rights to the patent rights that protect our core gene editing technology, and we must continue to satisfy our contractual obligations under the IMA in order to maintain the effectiveness of the consents by California and Vienna to our license from Dr. Charpentier.

In the United States, each co-owner has the freedom to license and exploit the technology. As a result, we do not have exclusive access to any intellectual property rights that Dr. Charpentier co-owns with another entity, such as California and Vienna. Our license with Dr. Charpentier is therefore non-exclusive with respect to such co-owned rights. Furthermore, in the United States each co-owner is required to be joined as a party to any claim or action we may wish to bring to enforce those patent rights. Moreover, in the United States, non-exclusive licenses have no standing to bring a patent infringement action before a court. Therefore, for the patents owned with California and Vienna we have no ability to pursue third-party infringement claims without cooperation of California and Vienna and potentially their licensees. Although we have entered into the IMA with Vienna and California and their licensees, which provides for, among other things, notice of and coordination in the event of third-party infringement of the patent rights within the Patent Portfolio, there can be no assurance that Vienna and California will cooperate with us in any future infringement. If we are unable to enforce our core patent rights licensed from Dr. Charpentier, we may be unable to prevent third parties from competing with us and may be unable to persuade companies to sublicense our technology, either of which could have a material adverse effect on our business.

We May Experience Disputes With The Third Parties That We In-license Intellectual Property Rights From Or Those We License Intellectual Property To. Any Disputes With These Parties Could Adversely Affect Our Business And We Could Lose License Rights That Are Important To Our Business.

We license the intellectual property that covers our gene editing technology from a third party, and we expect to continue to in-license additional third-party intellectual property rights as we expand our gene editing technology. Disputes may arise with the third parties from whom we license our intellectual property rights from for a variety of reasons, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on, or derive from, intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships and obligations associated with sublicensing;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties, or maintain consents under the IMA, are complex, and certain provisions in such agreements may be susceptible to multiple interpretations, or may conflict in such a way that puts us in breach of one or more agreements, which would make us susceptible to lengthy and

expensive disputes with one or more of our licensing partners or the parties to the IMA. 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, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

Similarly, as we continue to enter into license agreements, collaboration agreements and partnerships with third-parties to expand our development programs, we have, and expect to continue to, out-license some of our intellectual property to these third-parties. Disputes may arise with these third parties to whom we out-license our intellectual property rights for a variety of reasons, including, the scope of rights granted under any such agreement and other interpretation-related issues. Any disputes with our current or future collaboration partners or licensees regarding the scope of intellectual property rights granted to such partner or licensee by us could result in the delay of development programs and would make us susceptible to lengthy and expensive disputes with our partners or licensees.

We May Not Be Successful In Obtaining Or Maintaining Necessary Rights To Any Product Candidates or Other Technologies We May Develop Through Acquisitions And In-Licenses.

We currently have rights to intellectual property, through in-licenses from third parties, to identify and develop product candidates, as well as use other technologies. Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of gene editing technology and filing patent applications potentially relevant to our business. For example, we are aware of several third-party patent applications that, if issued, may be construed to cover our gene editing technology and product candidates. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses from such third-party intellectual property holders. We may also require licenses from third parties for certain modified or improved components of gene editing technology, such as modified nucleic acids, as well as non-CRISPR/Cas9 technologies such as delivery methods that we are evaluating for use with product candidates we may develop. In addition, with respect to any patents we co-own with third parties, we may require licenses to such co-owners' interest to such patents. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for product candidates we may develop and gene editing technology. The licensing or acquisition of third-party intellectual property rights is a competitive area, and companies that may be more established, or have greater resources than we do may be pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. More established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates or technology that we may seek to acquire. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program, technology, or product candidate, or discontinue the practice of our core CRISPR/Cas9 gene editing technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Issued Patents Covering Our Technology And Product Candidates Could Be Found Invalid Or Unenforceable If Challenged In Court or before the USPTO or comparable foreign authority.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering a product candidate we may develop or our technology, including CRISPR/Cas9, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution.

Third parties have raised challenges to the validity of certain of our in-licensed patent applications, such as our in-licensed CRISPR/Cas9 patent applications in the context of third-party observations and oppositions filed in Europe and Australia, and may in the future raise similar claims related to our in-licensed and owned patent applications and patents before administrative bodies in the United States or in other jurisdictions, even outside the context of litigation. Mechanisms for challenging the validity of patents in patent offices include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in non-U.S. jurisdictions (e.g., opposition proceedings). Such proceedings could – after exhausting available appeals – result in the loss of our patent applications or patents, or their narrowing in such a way that they no longer cover our technology or platform, or any product candidates that we may develop. The outcome following legal assertions of invalidity and

unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our technology or platform, or any product candidates that we may develop. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects.

The Intellectual Property Landscape Around Gene Editing Technology, Including CRISPR/Cas9, Is Highly Dynamic, And Third Parties May Initiate And Prevail In Legal Proceedings Alleging That The Patents That We In-License Or Own Are Invalid Or That We Are Infringing, Misappropriating, Or Otherwise Violating Their Intellectual Property Rights, The Outcome Of Which Would Be Uncertain And Could Have A Material Adverse Effect On The Success Of Our Business.

The field of gene editing, especially in the area of gene editing technology, is still in its infancy, and no such products have reached the market. Due to the intense research and development that is taking place by several companies, including us and our competitors, in this field, the intellectual property landscape is in flux, and it may remain uncertain for the coming years. There may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market, and sell any product candidates that we may develop and use our proprietary technologies without infringing, misappropriating, or otherwise violating the intellectual property and proprietary rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. We are subject to and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and any product candidates we may develop, including re-examination interference proceedings, post-grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in other jurisdictions such as oppositions before the European Patent Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. If we are unable to prove that these patents are invalid and we are not able to obtain or maintain a license on commercially reasonable terms, such patents could have a material adverse effect on the conduct of our business. If we are found to infringe such third-party patents, we and our partners may be required to pay damages, cease commercialization of the infringing technology, including our core CRISPR/Cas9 gene editing technology, or obtain a license from such third parties, which may not be available on commercially reasonable terms or at all.

Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability, ownership, or priority. A court of competent jurisdiction could hold that these third-party patents are valid, enforceable, and infringed, which could materially and adversely affect our ability to commercialize any product candidates we may develop and any other product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's intellectual property rights, and we are unsuccessful in demonstrating that such patents are invalid or unenforceable, we could be required to obtain a license from such third party to continue developing, manufacturing, and marketing any product candidates we may develop and our technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We also could be forced, including by court order, to cease developing, manufacturing, and commercializing the infringing technology or product candidates. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations, and prospects.

Intellectual Property Litigation Could Cause Us To Spend Substantial Resources And Distract Our Personnel From Their Normal Responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time-consuming and is likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities and generally harm our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation in certain countries, including the United States, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing or misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Some Intellectual Property Which We Have In-licensed May Have Been Discovered Through Government Funded Programs And Thus May Be Subject To Federal Regulations Such As "march-in" Rights, Certain Reporting Requirements And A Preference For U.S.-based Manufacturers. Compliance With Such Regulations May Limit Our Exclusive Rights, And Limit Our Ability To Contract With Non-U.S. Manufacturers.

The intellectual property rights to which we have in-licensed under Dr. Charpentier's joint interest are co-owned by California, which has indicated that one or more of the inventions were made under Grant No. GM081879 awarded by the National Institute of Health. These rights are therefore subject to certain federal regulations. The U.S. government has certain rights pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act, to patents covering government rights in certain inventions developed under a government-funded program. These rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations, also referred to as "march-in rights." The U.S. government also has the right to take title to these inventions if we, or the applicable contractor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable contractor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future patents covering inventions is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

We May Not Be Able To Protect Our Intellectual Property And Proprietary Rights Throughout The World.

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in intellectual property laws various jurisdictions worldwide. Additionally, the patent laws of some countries do not afford intellectual property protection to the same extent as the laws of the United States. For example, unlike patent law in the United States, the patent law in Europe and many other jurisdictions precludes the patentability of methods of treatment of the human body and imposes substantial restrictions on the scope of claims it will grant if broader than specifically disclosed embodiments.

Many companies have encountered significant problems in protecting and defending intellectual property rights in various jurisdictions globally. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in various jurisdictions globally could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government

contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Changes To The Patent Law In The United States And Other Jurisdictions Could Diminish The Value Of Patents In General, Thereby Impairing Our Ability To Protect Our Product Candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. In addition, the Leahy-Smith Act has transformed the U.S. patent system into a "first to file" system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business, results of operations and financial condition.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. For example, in *Association for Molecular Pathology v. Myriad Genetics, Inc*., the Supreme Court ruled that a "naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," and invalidated Myriad Genetics' claims on the isolated BRCA1 and BRCA2 genes. Certain claims of our patents relate to CRISPR/Cas9 gene editing technology as well as guide components that are directed to naturally occurring DNA sequences. To the extent that such claims are deemed to be directed to natural products, or to lack an inventive concept above and beyond an isolated natural product, a court may decide the claims are invalid under *Myriad*. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Europe's planned Unified Patent Court may particularly present uncertainties for our ability to protect and enforce our patent rights against competitors in Europe. While that new court is being implemented to provide more certainty and efficiency to patent enforcement throughout Europe, it will also provide our competitors with a new forum to use to centrally revoke our European patents. It will be several years before we will understand the scope of patent rights that will be recognized and the strength of patent remedies that will be provided by that court. We will have the right to opt our patents out of that system over the first seven years of the court, but doing so may preclude us from realizing the benefits of the new unified court.

Obtaining And Maintaining Our Patent Protection Depends On Compliance with Various Procedural, Document Submission, Fee Payment and Other Requirements Imposed by Governmental Patent Agencies, And Our Patent Protection Could be Reduced or Eliminated For Non-Compliance With These Requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. Although an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In any such event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

If We Are Unable To Protect The Confidentiality Of Our Trade Secrets, Our Business And Competitive Position Would Be Harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary and confidential information and to

maintain our competitive position. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to our technology platform, these trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel from academic to industry scientific positions.

We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect proprietary information. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, or misappropriation of our intellectual property by third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results, and financial condition. 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, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

If We Do Not Obtain Patent Term Extension And Data Exclusivity For Any Product Candidates We May Develop, Our Business May Be Materially Harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Action of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or if the term of any such extension is less than we request, we will be unable to rely on our patent position to forestall the marketing of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed.

Intellectual Property Rights Do Not Necessarily Address All Potential Threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make gene therapy products that are similar to any product candidates we may develop or utilize similar gene therapy technology but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;

- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations, and prospects.

We May Be Subject To Claims That Our Employees, Consultants, Or Advisors Have Wrongfully Used Or Disclosed Confidential Information Of Their Current Or Former Employers Or Other Third Parties Or Claims Asserting Ownership Of What We Regard As Our Own Intellectual Property.

Many of our employees, consultants, and advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed confidential information or intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer or other third party. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. 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. Such claims could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If Our Trademarks Are Not Adequately Protected, Then We May Not Be Able To Build Name Recognition In Our Markets Of Interest And Our Business May Be Adversely Affected.

If our trademarks are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected. Our unregistered trademarks may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks. Over the long term, if we are unable to successfully register our trademarks and establish name recognition based on our trademarks, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

Risks Related to The Ownership of Our Common Shares

We Have Broad Discretion In The Use Of Our Cash Reserves And May Not Use Such Cash Reserves Effectively.

Our management has broad discretion to use our cash reserves and could use our cash reserves in ways that do not improve our results of operations or enhance the value of our common shares. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common shares to decline, and delay the development of our product candidates. Pending their use, we may invest our cash reserves in a manner that does not produce income or that loses value.

Sales Of A Substantial Number Of Our Common Shares In The Public Market Could Cause Our Share Price To Fall.

Sales of a substantial number of our common shares in the public market or the perception that these sales might occur could depress the market price of our common shares, could make it more difficult for you to sell your common shares at a time and price that you deem appropriate and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common shares.

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 any earnings will be reinvested in our business and that no dividends will be paid prior to the time we have an established revenue stream to support continuing dividends. The proposal to pay future dividends to shareholders will in addition effectively be at the discretion of our board of directors and shareholders after taking into account various factors including our business prospects, cash requirements, financial performance and new product development. In addition, payment of future dividends is subject to certain limitations pursuant to Swiss law or by our articles of association. Accordingly, investors cannot rely on dividend income from our common shares and any returns on an investment in our common shares will likely depend entirely upon any future appreciation in the price of our common shares. Dividends, if any, paid on our common shares are subject to Swiss federal withholding tax, except if paid out of reserves from capital contributions, or *Kapitaleinlagen*.

We Are A Swiss Corporation. The Rights Of Our Shareholders May Be Different From The Rights Of Shareholders In Companies Governed By The Laws Of U.S. Jurisdictions.

We are a Swiss corporation. Our corporate affairs are governed by our articles of association and by Swiss law. The rights of our shareholders and the responsibilities of members of our board of directors may be different from the rights and obligations of shareholders and directors of companies governed by the laws of U.S. jurisdictions. In the performance of its duties, our board of directors is required by Swiss law to consider the interests of our Company, our shareholders and our employees with due observation of the principles of reasonableness and fairness. It is possible that the board of directors will consider interests that are different from, or in addition to, your interests as a shareholder. Swiss corporate law limits the ability of our shareholders to challenge resolutions made or other actions taken by our board of directors in court. Our shareholders generally are not permitted to file a suit to reverse a decision or an action taken by our board of directors but are instead only permitted to seek damages for breaches of the duty of care and loyalty. As a matter of Swiss law, shareholder claims against a member of our board of directors for breach of the duty of care and loyalty would have to be brought in Zug, Switzerland, or where the relevant member of our board of directors is domiciled. In addition, under Swiss law, any claims by our shareholders against us must be brought exclusively in Zug, Switzerland.

As A Swiss Corporation, We Are Subject To Swiss Legal Provisions That May Limit Our Flexibility To Swiftly Implement Certain Initiatives Or Strategies.

We are required, from time to time, to evaluate the carrying amount of our investments in affiliates, as presented on our Swiss standalone balance sheet. If we determine that the carrying amount of any such investment exceeds its fair value, we may conclude that such investment is impaired. The recognized loss associated with such a non-cash impairment could result in our net assets no longer covering our statutory share capital and statutory capital reserves. Under Swiss law, if our net assets cover less than 50 percent of our statutory share capital, statutory capital reserves and statutory earnings reserves that are not repayable to shareholders, the board of directors must take appropriate measure to overcome the situation and, if necessary, convene a general meeting of shareholders and propose measures to remedy such a capital loss. The appropriate measures depend on the relevant circumstances and the magnitude of the recognized loss and may include seeking shareholder approval for offsetting the aggregate loss, or a portion thereof, with our statutory capital reserves including qualifying additional paid-in capital otherwise available for distributions to shareholders or raising new equity. Depending on the circumstances, we may also need to use qualifying additional paid-in capital available for distributions in order to reduce our accumulated net loss and such use might reduce our ability to make distributions without subjecting our shareholders to Swiss withholding tax. These Swiss law requirements could limit our flexibility to swiftly implement certain initiatives or strategies.

Anti-takeover Provisions In Our Articles Of Association Could Make An Acquisition Of Our Company, Which May Be Beneficial To Our Shareholders, More Difficult And May Prevent Attempts By Our Shareholders To Replace Or Remove Our Current Management.

Provisions in our articles of association may discourage, delay or prevent an acquisition of our Company or changes in the composition of our board of directors. Among other things, these provisions require the approval of at least two thirds of represented shares present or voting at a shareholder meeting for the removal of a member of our board of directors and to increase the maximum number of members of our board of directors; limit the accumulated voting rights of any person or entity to 15% of our registered share capital; limit the voting rights of an acquirer of more than 5% of our registered share capital in a transaction or series of transactions in which our board of directors did not provide for an exemption, which could prevent or delay a change in control of our Company; provide that the board of directors is authorized, at any time during a maximum two-year period, which under our current

authorized share capital will expire on June 10, 2023 and will, if resolved by the shareholders' meeting, be replaced by a capital band (*Kapitalband*) (see "*Risk Factors—Our Status As A Swiss Corporation May Limit Our Flexibility With Respect To Certain Aspects Of Capital Management And May Cause Us To Be Unable To Make Distributions Without Subjecting Our Shareholders To Swiss Withholding Tax"*), to issue a specified number of shares, which under our current authorized share capital is approximately forty-nine percent of the share capital registered in the commercial register, and to limit or withdraw the preemptive rights of existing shareholders in various circumstances; provide for a conditional share capital that authorizes the issuance of additional shares up to a maximum amount of approximately thirty-two percent of the share capital registered in the commercial register, without obtaining additional shareholder approval, (i) through the exercise of conversion and/or option rights granted in connection with bonds or similar instruments, including convertible debt instruments, and (ii) in connection with the exercise of options granted to employees or other service providers of the Company or any of its subsidiaries; and provide that a merger or demerger transaction requires the affirmative vote of at least two thirds of the shares represented at a shareholders' meeting.

Although we believe these provisions collectively provide for an opportunity to obtain greater value for shareholders by requiring potential acquirors to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some shareholders. In addition, these provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Our Common Shares Are Issued Under The Laws Of Switzerland, Which May Not Protect Investors In A Similar Fashion Afforded By Incorporation In A U.S. State.

We are organized under the laws of Switzerland. However, there can be no assurance that Swiss law will not change in the future or that it will serve to protect investors in a similar fashion afforded under corporate law principles in the United States, which could adversely affect the rights of investors.

Our Status As A Swiss Corporation May Limit Our Flexibility With Respect To Certain Aspects Of Capital Management And May Cause Us To Be Unable To Make Distributions Without Subjecting Our Shareholders To Swiss Withholding Tax.

Our articles of association as in force allow our shareholders to authorize share capital that can be issued by the board of directors without additional shareholder approval. The authorized share capital approved by our shareholders will expire on June 10, 2023 and is limited to approximately forty-nine percent of our registered share capital pursuant to the articles of association in force. Pursuant to the Swiss corporate law reform effective January 1, 2023, a capital band (*Kapitalband*) was introduced as replacement of the authorized share capital. The authorized share capital as approved by the shareholders will thus, upon its expiry on June 10, 2023, need to be replaced by a capital band. Such capital band, if resolved by the shareholders' meeting, will authorize the board of directors to, within up to five years, increase or, subject to a respective resolution of the shareholders' meeting, also to decrease the share capital. This authorization is in each case limited to 50% of the existing registered share capital and must be renewed by the shareholders upon expiry of the respective term. Subject to specified exceptions, Swiss law grants preemptive rights to existing shareholders to subscribe to any new issuance of shares. Swiss law also does not provide as much flexibility in the various terms that can attach to different classes of shares as the laws of some other jurisdictions. Swiss law also reserves for approval by shareholders certain corporate actions over which a board of directors would have authority in some other jurisdictions. For example, the payment of dividends and the cancellation of treasury shares must be approved by shareholders. These Swiss law requirements relating to our capital management may limit our flexibility, and situations may arise where greater flexibility would have provided substantial benefits to our shareholders.

Under Swiss law, a Swiss corporation may pay dividends only if the corporation has sufficient distributable profits, or if the corporation has distributable reserves, each as evidenced by its audited standalone statutory balance sheet, and after allocations to reserves required by Swiss law and our articles of association have been deducted. Freely distributable reserves are generally booked either as "free reserves" or as "capital contributions" (*Kapitaleinlagen*, contributions received from shareholders) in the "reserve from capital contributions." Distributions may be made out of registered share capital—the aggregate par value of a company's registered shares—only by way of a capital reduction. We will not be able to pay dividends or make other distributions to shareholders on a Swiss withholding tax-free basis in excess of our aggregate qualifying contributions and registered share capital unless we increase our share capital or our reserves from capital contributions. We would also be able to pay dividends out of distributable profits or freely distributable reserves, but such dividends would be subject to Swiss withholding taxes. There can be no assurance that we will have sufficient distributable profits, free reserves, reserves from capital contributions or registered share capital to pay a dividend or effect a capital reduction, that our shareholders will approve dividends or capital reductions proposed by us or that we will be able to meet the other legal requirements for dividend payments or distributions as a result of capital reductions.

Dividends and similar cash or in-kind distributions made by the Company to a shareholder (including liquidation proceeds and stock dividends) are subject to Swiss withholding tax (*Verrechnungssteuer*), currently at a rate of 35% (applicable to the gross amount of the taxable distribution). The Company is obliged to deduct the Swiss withholding tax from the gross amount of any taxable distribution and to pay the tax to the Swiss Federal Tax Administration within 30 calendar days of the due date of such distribution.

However, the repayment of the nominal value of the shares and any repayment of qualifying additional paid-in capital (capital contribution reserves (*Reserven aus Kapitaleinlagen*)) are not subject to Swiss withholding tax. The Swiss withholding tax will also apply to payments (exceeding the respective share capital and used capital contribution reserves) upon a repurchase of shares by the Company, (i) if the Company's share capital is reduced upon such repurchase (redemption of shares), (ii) if the total of repurchased shares exceeds 10% of the Company's share capital or (iii) if the repurchased shares are not resold within six years after the repurchase. This six-year deadline to resell the repurchased shares is suspended for so long as the shares are reserved to cover obligations under convertible bonds, option bonds or employee stock option plans (in the case of employee stock option plans, the maximum suspension is six years). In the event of a taxable share repurchase, Swiss withholding tax is imposed on the difference between the repurchase price and the sum of the nominal value of the repurchased shares and capita contribution reserves paid back upon the repurchase.

Swiss resident individuals who hold their shares as private assets, or Resident Private Shareholders, are in principle eligible for a full refund or credit against income tax of the Swiss withholding tax if they duly report the underlying income in their income tax return. In addition, (i) corporate and individual shareholders who are resident in Switzerland for tax purposes, (ii) corporate and individual shareholders who are not resident in Switzerland, and who, in each case, hold their shares as part of a trade or business carried on in Switzerland through a permanent establishment with fixed place of business situated in Switzerland for tax purposes and (iii) Swiss resident private individuals who, for income tax purposes, are classified as "professional securities dealers" for reasons of, inter alia, frequent dealing, or leveraged investments, in shares and other securities (collectively, "Domestic Commercial Shareholders") are in principle eligible for a full refund or credit against income tax of the Swiss withholding tax if they duly report the underlying income in their income statements or income tax return, as the case may be.

Shareholders who are not resident in Switzerland for tax purposes, and who, during the respective taxation year, have not engaged in a trade or business carried on through a permanent establishment with fixed place of business situated in Switzerland for tax purposes, and who are not subject to corporate or individual income taxation in Switzerland for any other reason (collectively, "Non-Resident Shareholders") may be entitled to a total or partial refund of the Swiss withholding tax if the country in which such recipient resides for tax purposes maintains a bilateral treaty, or Tax Treaty, for the avoidance of double taxation with Switzerland and further conditions of such Tax Treaty are met.

A U.S. shareholder that qualifies for benefits under the U.S.-Swiss Tax Treaty, may apply for a refund of the tax withheld in excess of the 15% treaty rate (or in excess of the 5% reduced treaty rate for qualifying corporate shareholders with at least 10% voting rights, or for a full refund in the case of qualified pension funds). Non-Resident Shareholders should be aware that the procedures for claiming treaty benefits (and the time required for obtaining a refund) may differ from country to country. Non-Resident Shareholders should consult their own legal, financial or tax advisors regarding receipt, ownership, purchases, sale or other dispositions of shares and the procedures for claiming a refund of the Swiss withholding tax.

Certain U.S. Shareholders May Be Subject To Adverse U.S. Federal Income Tax Consequences If We Are A Controlled Foreign Corporation.

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for United States federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income" and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents and royalties, gains from the sale of securities and income from certain transactions with related parties. For tax years beginning after December 31, 2017, each Ten Percent Shareholder of a CFC is also required to include in income such Ten Percent Shareholder's share of "global intangible low-taxed income" with respect to such CFC. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for United States federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the U.S. Internal Revenue Code of 1986, as amended, or the Code, who owns or is considered to own 10% or more of (1) the total combined voting power of all classes of stock entitled to vote or (2) the value of all classes of stock of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain.

During our 2022 taxable year we believe that we had certain shareholders that were Ten Percent Shareholders for U.S. federal income tax purposes. However, our CFC status for the taxable year ending on December 31, 2022 and our current taxable year is unknown and we may be a CFC for the taxable year ending on December 31, 2022, our current taxable year or a following year. In addition, recent changes to the attribution rules relation to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. Furthermore, it is possible that our non-United States subsidiaries will be CFCs for the current taxable year or a future taxable year even if we are not a CFC for such taxable year(s). U.S. holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a

CFC and a passive foreign investment company, or PFIC, we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Certain U.S. Shareholders May Suffer Adverse Tax Consequences If We Are Characterized As A Passive Foreign Investment Company.

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

Our status as a PFIC will depend on the composition of our income and the composition and value of our assets which may be determined in part by reference to the quarterly market value of our common shares, which may be volatile. Our status may also depend, in part, on how, and how quickly, we utilize the cash proceeds from prior offerings in our business. Our status as a PFIC is a fact-intensive determination made on an annual basis and we cannot provide any assurances regarding our PFIC status for any past, current or future taxable years.

Because it is possible we were a PFIC for the 2021 taxable year, we provided information necessary for our shareholders to make a qualified electing fund, or QEF, election with respect to us for the 2021 taxable year. We provided such information on our website (www.crisprtx.com). A U.S. holder that makes a QEF election with respect to our shares is required to include a pro rata share of our income on a current basis, whether or not we make distributions. For the 2021 taxable year, the Company-wide amount of ordinary earnings and net capital gain for purposes of the QEF inclusion rules was $504.7 million of ordinary earnings and $0.0 net capital gain, and we may have material amounts of ordinary earnings and/or net capital gain for purposes of the QEF inclusion rules in the 2022 taxable year or future taxable years. Although we have not yet determined whether we are a PFIC for the 2021 taxable year or the current taxable year, it is possible that we may be a PFIC for the 2021 taxable year and / or current taxable year as well. We will endeavor to provide to you, for each taxable year that we are or may be a PFIC, a PFIC Annual Information Statement containing information necessary for you to make a QEF election with respect to us. Alternatively, a U.S. holder may be able to make a mark-to-market election, assuming that our shares constitute "marketable" securities under the Code, which generally avoids the adverse consequences of PFIC status discussed above, but would require a U.S. holder to annually report as ordinary income any increase in value of our shares during the year (as well as generally allowing deductions for any decrease in the value of our shares).

If we are determined to be a PFIC, a U.S. holder will generally be treated as owning a proportionate amount (by value) of shares owned by us in any of our direct or indirect subsidiaries that are also PFICs, each a lower-tier PFIC, and will be subject to similar adverse rules with respect to distributions from, or dispositions of, such lower-tier PFICs, in each case as if such U.S. holder held such shares directly (even if such U.S. holder does not receive the proceeds of such distributions or dispositions directly). We have not determined whether any of our subsidiaries (including TRACR and CRISPR Therapeutics Ltd.) are or may be lower-tier PFICs for any prior taxable year, the current taxable year or future taxable years, and we do not intend to do so. We also do not intend to make available the information necessary for U.S. holders to make a QEF election with respect to any lower-tier PFICs and therefore you should expect that you will not be able to make a QEF election with respect to them. You are urged to consult your own tax advisors regarding our PFIC status and the tax considerations relevant to an investment in a PFIC, including the availability, and advisability, of, and procedure for making, a QEF election or a mark to market election with respect to us, and the application of the PFIC rules to any of our subsidiaries.

U.S. Shareholders May Not Be Able To Obtain Judgments Or Enforce Civil Liabilities Against Us Or Our Executive Officers Or Members Of Our Board Of Directors.

We are organized under the laws of Switzerland and our registered office and domicile is located in Zug, Switzerland. Moreover, certain of our directors and executive officers are not residents of the United States, and all or a substantial portion of the assets of such persons are located outside the United States. As a result, it may not be possible for investors to effect service of process within the United States upon us or upon such persons or to enforce against them judgments obtained in U.S. courts, including judgments in actions predicated upon the civil liability provisions of the federal securities laws of the United States. We have been advised by our Swiss counsel that there is doubt as to the enforceability in Switzerland of original actions, or in actions for enforcement of judgments of U.S. courts, of civil liabilities to the extent solely predicated upon the federal and state securities laws of the United States. Original actions against persons in Switzerland based solely upon the U.S. federal or state securities laws are governed, among other things, by the principles set forth in the Swiss Federal Act on Private International Law. This statute provides that the application of provisions of non-Swiss law by the courts in Switzerland shall be precluded if the result is incompatible with

Swiss public policy. Also, mandatory provisions of Swiss law may be applicable regardless of any other law that would otherwise apply.

Switzerland and the United States do not have a treaty providing for reciprocal recognition and enforcement of judgments in civil and commercial matters. The recognition and enforcement of a judgment of the courts of the United States in Switzerland is governed by the principles set forth in the Swiss Federal Act on Private International Law. This statute provides in principle that a judgment rendered by a non-Swiss court may be enforced in Switzerland only if:

- the non-Swiss court had jurisdiction pursuant to the Swiss Federal Act on Private International Law;
- the judgment of such non-Swiss court has become final and non-appealable;
- the judgment does not contravene Swiss public policy;
- the court procedures and the service of documents leading to the judgment were in accordance with the due process of law; and
- no proceeding involving the same position and the same subject matter was first brought in Switzerland, or adjudicated in Switzerland, or was earlier adjudicated in a third state and this decision is recognizable in Switzerland.

General Risks

We Incur Significant Costs As A Result Of Operating As A Public Company And Our Management Is Required To Devote Substantial Time To Compliance Initiatives And Corporate Governance Practices.

As a public company, we incur significant legal, accounting and other expenses. SOX, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Market, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time towards maintaining compliance with these requirements. Moreover, these requirements increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to SOX Section 404, we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In this regard, we incur substantial accounting expenses and expend significant management efforts. Our testing may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or significant deficiencies. If we identify one or more material weaknesses, or significant deficiencies that we cannot remediate in a timely manner, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

The Market Price Of Our Common Shares Has Been Volatile and Fluctuate Substantially, Which Could Result In Substantial Losses For Shareholders.

Our share price has been, and in the future may be, subject to substantial volatility. In addition, the stock market in general, and Nasdaq listed biopharmaceutical companies in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. For example, our shares traded within a range of a high price of $220.20 and a low price of $11.63 per share for the period beginning on October 19, 2016, our first day of trading on the Nasdaq Global Market, through December 31, 2022. As a result of this volatility, our shareholders could incur substantial losses. In addition, the market price for our common shares may be influenced by many factors, including:

- the success of existing or new competitive products or technologies;
- the timing and results of any product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure or discontinuation of any of our product development and research programs;
- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- developments or changing views regarding the use of genomic products, including those that involve gene editing;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;

- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- 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;
- announcement or expectation of additional financing efforts;
- sales of our common shares by us, our insiders, or other shareholders;
- expiration of market stand-off or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our common shares;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

These and other market and industry factors may cause the market price and demand for our common shares to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their common shares and may otherwise negatively affect the liquidity of our common shares. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of our management.

Unfavorable Global Economic Conditions Could Adversely Affect Our Business, Financial Condition Or Results Of Operations.

Our results of operations could be adversely affected by general conditions in the global economy, disruption of global financial markets and a recession or market correction, including, for example, as a result of the coronavirus pandemic, the ongoing military conflict between Russia and Ukraine and the related sanctions imposed against Russia, and other global macroeconomic factors such as inflation. Such conditions could reduce our ability to access capital, which could in the future negatively affect our liquidity and could materially affect our business and the value of our common stock.

If Securities Analysts Do Not Publish Research Or Reports About Our Business Or If They Publish Negative Evaluations Of Our Common Shares, The Price Of Our Common Shares Could Decline.

The trading market for our common shares will rely in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our common shares, the price of our common shares could decline. If one or more of these analysts cease to cover our common shares, we could lose visibility in the market for our common shares, which in turn could cause our common share price to decline.

Our Business Is Subject To Economic, Political, Regulatory And Other Risks Associated With International Operations.

Our business is subject to risks associated with conducting business internationally. We and a number of our suppliers and collaborative and clinical study relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing regulatory requirements for drug approvals in non-U.S. countries;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates and currency controls;

- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling outside the United States;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities outside the United States;
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including floods and fires; and
- adverse effects and instability in global financial markets, political institutions and regulatory agencies resulting from the United Kingdom's June 23, 2016 vote to leave the EU, subsequent invocation of Article 50 of the Lisbon Treaty on March 29, 2017, and the United Kingdom is formally leaving the EU on January 31, 2020.

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. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company and our vendors, including personal information of our employees and study subjects, and company and vendor confidential data. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our personnel or the personnel of our vendors to disclose sensitive information in order to gain access to our data and/or systems. We may experience threats to our data and systems, including malicious codes and viruses, phishing and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our information technology systems or those of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive practices. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. As we outsource more of our information systems to vendors, engage in more electronic transactions with payors and patients, and rely more on cloud-based information systems, the related security risks will increase and we will need to expend additional resources to protect our technology and information systems. In addition, there can be no assurance that our internal information technology systems or those of our third-party contractors, or our consultants' efforts to implement adequate security and control measures, will be sufficient to protect us against breakdowns, service disruption, data deterioration or loss in the event of a system malfunction, or prevent data from being stolen or corrupted in the event of a cyberattack, security breach, industrial espionage attacks or insider threat attacks which could result in financial, legal, business or reputational harm.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal executive offices are located in Zug, Switzerland pursuant to a real estate lease agreement with a term that renews every three months. Our U.S. headquarters for research and development is located at 105 West First Street, Boston, Massachusetts where we lease approximately 263,500 square feet of laboratory and office space. The facility is leased through October 2034 with an option to extend the term of the lease for two additional five-year periods.

In May 2020, we entered into a lease agreement for a 50,249 square foot building in Framingham, Massachusetts, which we are using as a cell therapy manufacturing facility for clinical production, and plan to use for commercial production, of our investigational cell therapy product candidates. This facility is leased through March 2036 with an option to extend the term of the lease for two additional seven-year periods.

We also lease business offices elsewhere in Cambridge, Massachusetts, San Francisco, California and London, United Kingdom. We believe that our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Item 3. Legal Proceedings.

In the ordinary course of business, we are from time to time involved in lawsuits, investigations, proceedings and threats of litigation related to, among other things, our intellectual property estate (including the Patent Portfolio), commercial arrangements and other matters. Such proceedings may include quasi-litigation, inter partes administrative proceedings in the U.S. Patent and Trademark Office and the European Patent Office involving our intellectual property estate including the Patent Portfolio. The outcome of any of the foregoing, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. If we were unable to prevail in any such proceedings, our business, results of operations, liquidity and financial condition could be adversely affected.

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.

Market Information

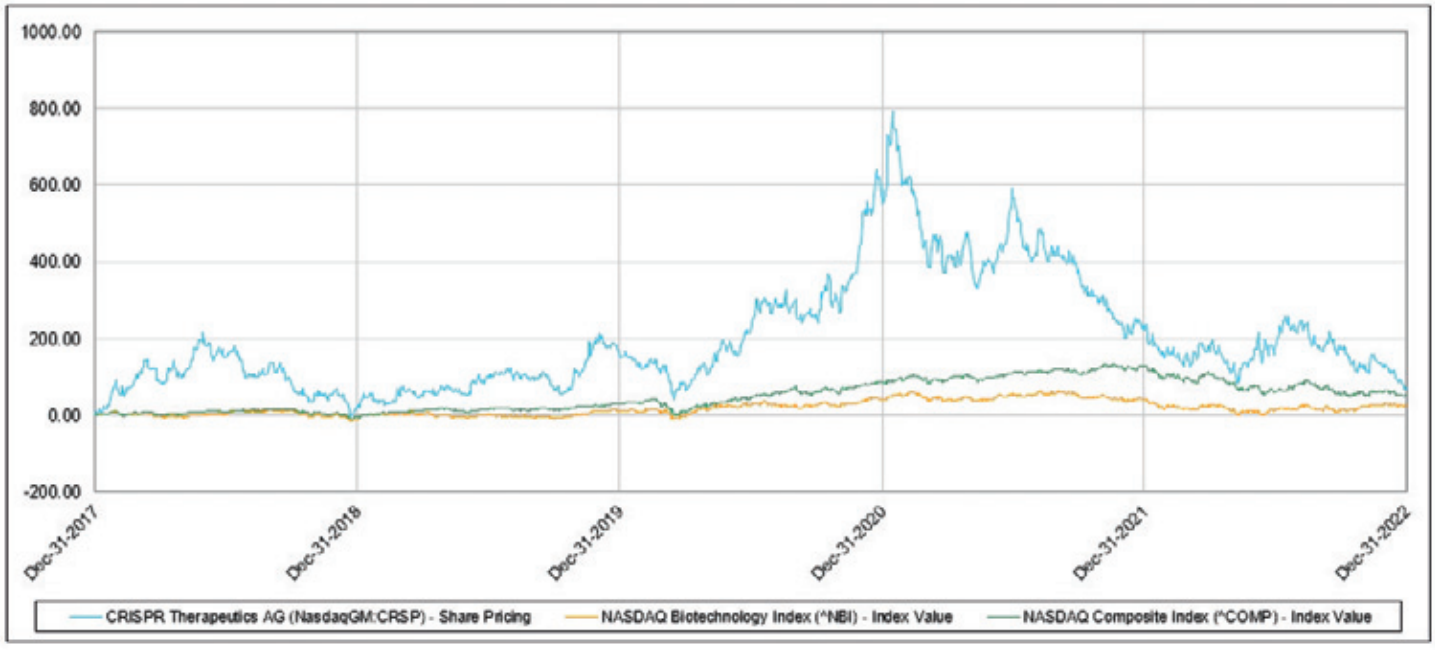
Our common shares are traded on The Nasdaq Global Market under the symbol "CRSP."

Stock Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the Securities and Exchange Commission, or SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, nor shall such information be incorporated by reference into any future filing under the Exchange Act or Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The graph set forth below compares the cumulative total stockholder return on our shares between December 31, 2017 and December 31, 2022, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 on December 31, 2017 in our common shares, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The comparisons shown in the graph below are based upon historical data. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

Comparison of Total Return Among CRISPR Therapeutics AG, the NASDAQ Composite Index and the NASDAQ Biotechnology Index



Swiss Tax Considerations

Swiss Withholding Tax

Under present Swiss tax law, dividends due and similar cash or in-kind distributions made by us to a shareholder (including liquidation proceeds and stock dividends) are subject to Swiss federal withholding tax (*Verrechnungssteuer*) ("Withholding Tax"), currently at a rate of 35% (applicable to the gross amount of the taxable distribution). We are obliged to deduct the Withholding Tax from the gross amount of any taxable distribution and to pay the tax to the Swiss Federal Tax Administration within 30 calendar days of the due date of such distribution. However, the repayment of the nominal value of shares and any repayment of qualifying additional paid-in capital (capital contribution reserves (*Reserven aus Kapitaleinlagen*)) are not subject to the Withholding Tax. The Withholding Tax will also apply to payments (exceeding the respective share capital and used capital contribution reserves) upon a repurchase of shares by us, (i) if our share capital is reduced upon such repurchase (redemption of shares), (ii) if the total of repurchased shares exceeds 10% of our share capital or (iii) if the repurchased shares are not resold within six years after the repurchase. This six year deadline to resell the repurchased shares is suspended for so long as the shares are reserved to cover obligations under convertible bonds, option bonds or employee stock option plans (in the case of employee stock option plans, the maximum suspension is six years). In the event of a taxable share repurchase, Withholding Tax is imposed on the difference between the repurchase price and the sum of the nominal value of the repurchased shares and qualifying additional paid-in capital paid back upon the repurchase.

Swiss resident individuals who hold their shares as private assets ("Resident Private Shareholders") are in principle eligible for a full refund or credit against income tax of the Withholding Tax if they duly report the underlying income in their income tax return. In addition, (i) corporate and individual shareholders who are resident in Switzerland for tax purposes, (ii) corporate and individual shareholders who are not resident in Switzerland, and who, in each case, hold their shares as part of a trade or business carried on in Switzerland through a permanent establishment with fixed place of business situated in Switzerland for tax purposes and (iii) Swiss resident private individuals who, for income tax purposes, are classified as "professional securities dealers" for reasons of, inter alia, frequent dealing, or leveraged investments, in shares and other securities (collectively, "Domestic Commercial Shareholders") are in principle eligible for a full refund or credit against income tax of the Withholding Tax if they duly report the underlying income in their income statements or income tax return, as the case may be.

Shareholders who are not resident in Switzerland for tax purposes, and who, during the respective taxation year, have not engaged in a trade or business carried on through a permanent establishment with fixed place of business situated in Switzerland for tax purposes, and who are not subject to corporate or individual income taxation in Switzerland for any other reason (collectively, "Non-Resident Shareholders") may be entitled to a total or partial refund of the Withholding Tax if the country in which such recipient resides for tax purposes maintains a bilateral treaty for the avoidance of double taxation with Switzerland ("Tax Treaty") and further conditions of such Tax Treaty are met. Non-Resident Shareholders should be aware that the procedures for claiming treaty benefits (and the time required for obtaining a refund) may differ from country to country. Non-Resident Shareholders should consult their own legal, financial or tax advisors regarding receipt, ownership, purchases, sale or other dispositions of shares and the procedures for claiming a refund of the Withholding Tax.

Automatic Exchange of Information

The Automatic Exchange of Information in Tax Matters (the "AEI") is a global initiative led by the Organization for Economic Co-operation and Development. It aims to establish a universal standard for automatic exchange of tax information and to increase tax transparency.

Jurisdictions that are committed to implement or have implemented the AEI (such as Switzerland, the EU member countries and many other jurisdictions worldwide) require their Reporting Financial Institutions in accordance with the respective local implementing law to determine the tax residence(s) of their account holders and controlling persons (as applicable) and, in case of reportable accounts, report certain identification information, account information and financial information (including the account balance and related payments such as interest, dividends, other income and gross proceeds) to the local tax authority which will then exchange the information received with the tax authorities in the relevant reportable jurisdictions.

A list of the AEI agreements of Switzerland in effect or signed and becoming effective can be found on the website of the State Secretariat for International Financial Matters.

Swiss Federal Stamp Taxes

The issuance of the shares and the sale pursuant to and in the course of an offering is subject to Swiss federal securities issuance stamp tax (*Emissionsabgabe*) of 1% and would be borne by us.

The subsequent purchase or sale of our shares, whether by Resident Private Shareholders, Domestic Commercial Shareholders or Non-Resident Shareholders (secondary market transactions), may be subject to the Swiss federal securities transfer stamp tax (*Umsatzabgabe*) at a current rate of up to 0.15%, calculated on the purchase price or the sale proceeds, respectively, if (i) such transfer occurs through or with a Swiss or Liechtenstein bank or by or with involvement of another Swiss securities dealer as defined in the Swiss federal stamp tax duty act and (ii) no exemption applies.

Swiss Federal, Cantonal and Communal Individual Income Tax and Corporate Income Tax

*Non-Resident Shareholder*s

Non-Resident Shareholders are not subject to any Swiss federal, cantonal or communal income tax on dividend payments and similar distributions because of the mere holding of our shares. The same applies for capital gains on the sale of shares. For Withholding Tax consequences, see above.

Resident Private Shareholders and Domestic Commercial Shareholders

Resident Private Shareholders who receive dividends and similar cash or in-kind distributions (including liquidation proceeds as well as stock dividends or taxable repurchases of shares as described above), which are not repayments of the nominal value of the shares or qualifying additional paid-in capital, are required to report such receipts in their individual income tax returns and are subject to Swiss federal, cantonal and communal income tax on any net taxable income for the relevant tax period. Furthermore, for Swiss federal individual income tax purposes, dividends and similar distributions as described above are only taxed at 70% on federal level (*Teilbesteuerung*), if the investment amounts to at least 10% of our share capital. On cantonal and communal level similar provisions were introduced but the regulations may vary, depending on the canton of residency.

A gain or a loss by Resident Private Shareholders realized upon the sale or other disposition of shares to a third party will generally be a tax-free private capital gain or a not tax-deductible capital loss, as the case may be.

Domestic Commercial Shareholders who receive dividends and similar cash or in-kind distributions (including liquidation proceeds as well as bonus shares) are required to recognize such payments in their income statements for the relevant tax period and are subject to Swiss federal, cantonal and communal individual or corporate income tax, as the case may be, on any net taxable earnings accumulated (including the dividends) for such period. Domestic Commercial Shareholders who are corporate taxpayers may qualify for participation relief on dividend distributions (*Beteiligungsabzug*), if shares held have a market value of at least CHF 1 million or represent at least 10% of our share capital or give entitlement to at least 10% of our profit and reserves, respectively.

Domestic Commercial Shareholders are required to recognize a gain or loss realized upon the disposal of shares in their income statement for the respective taxation period and are subject to Swiss federal, cantonal and communal individual or corporate income tax, as the case may be, on any net taxable earnings (including the gain or loss realized on the sale or other disposition of shares) for such taxation period. For Domestic Commercial Shareholders who are individual taxpayers, a gain realized upon the disposal of shares is taxed at 70% on federal level (*Teilbesteuerung*), if (i) the investment is held in connection with the conduct of a trade or business or qualifies as an opted business asset (*gewillkürtes Geschäftsvermögen*) according to Swiss tax law, (ii) the sold shares reflect an interest in the share capital of a company of at least 10% and (iii) were held for at least one year. On cantonal and communal level similar provisions were introduced, but the regulations may vary depending on the canton of residency. Domestic Commercial Shareholders who are corporate taxpayers may be entitled to participation relief (*Beteiligungsabzug*), if shares sold during the tax period (i) reflect an interest in the share capital of a company of at least 10% or if such shares sold allow for at least 10% of the profit and reserves and (ii) were held for at least one year. The participation relief applies to the difference between the sale proceeds and the initial costs of the participation (*Gestehungskosten*), resulting in the taxation of a recapture of previous write-downs of the participation.

Swiss Wealth Tax and Capital Tax

Non-Resident Shareholders

Non-Resident Shareholders holding our shares are not subject to cantonal and communal wealth or annual capital tax because of the mere holding of such shares.

Resident Private Shareholders and Domestic Commercial Shareholders

Resident Private Shareholders are required to report their shares as part of their private wealth and are subject to cantonal and communal wealth tax. Domestic Commercial Shareholders are required to report their shares as part of their business wealth or taxable capital, as defined, and are subject to cantonal and communal wealth or annual capital tax.

Swiss Facilitation of the Implementation of the U.S. Foreign Account Tax Compliance Act

Switzerland has concluded an intergovernmental agreement with the United States to facilitate the implementation of the Foreign Account Tax Compliance Act. The agreement ensures that the accounts held by U.S. persons with Swiss financial institutions are disclosed to the U.S. tax authorities either with the consent of the account holder or by means of group requests within the scope of administrative assistance. Information will not be transferred automatically in the absence of consent, and instead will be exchanged only within the scope of administrative assistance on the basis of the double taxation agreement between the United States and Switzerland. On October 8, 2014, the Swiss Federal Council approved a mandate for negotiations with the United States on changing the current direct notification-based regime to a regime where the relevant information is sent to the Swiss Federal Tax Administration, which in turn provides the information to the U.S. tax authorities.

THE DISCUSSION ABOVE IS A SUMMARY OF MATERIAL SWISS TAX CONSIDERATIONS. IT DOES NOT COVER ALL TAX MATTERS THAT MAY BE OF IMPORTANCE TO A PARTICULAR SHAREHOLDER. EACH SHAREHOLDER IS URGED TO CONSULT ITS OWN TAX ADVISOR ABOUT THE TAX CONSEQUENCES TO IT IN LIGHT OF THE SHAREHOLDER'S OWN CIRCUMSTANCES.

Holders

As of February 16, 2023, we had approximately 19 holders of record of our common shares. This number does not include beneficial owners whose shares were held in street name.

Dividends

We have not paid any cash dividends on our common shares since inception and do not anticipate paying cash dividends in the foreseeable future.

Securities authorized for issuance under equity compensation plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Item 6. Reserved

Not applicable.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a leading gene editing company focused on the development of CRISPR/Cas9-based therapeutics. CRISPR/Cas9 is a revolutionary gene editing technology that allows for precise, directed changes to genomic DNA. The application of CRISPR/Cas9 for gene editing was co-invented by one of our scientific founders, Dr. Emmanuelle Charpentier. Dr. Charpentier and her collaborators published work elucidating how CRISPR/Cas9, a naturally occurring viral defense mechanism found in bacteria, can be adapted for use in gene editing. We are applying this technology to potentially treat a broad set of rare and common diseases. We believe that our scientific expertise, together with our gene editing approach, may enable an entirely new class of highly active and potentially curative therapies for patients, including those for whom current biopharmaceutical approaches have had limited success.

We have established a portfolio of therapeutic programs in a broad range of disease areas across four core franchises: hemoglobinopathies, immuno-oncology, regenerative medicine and *in vivo* approaches. Our most advanced programs target the genetically defined diseases transfusion-dependent beta thalassemia, or TDT, and severe sickle cell disease, or SCD, two hemoglobinopathies with high unmet medical need. We are also progressing several gene-edited allogeneic cell therapy programs, including allogeneic chimeric antigen receptor T cell, or CAR T, candidates for the treatment of hematological and solid tumor

cancers, and investigational, allogeneic, gene-edited, immune-evasive, stem cell-derived therapies for the treatment of type 1 diabetes, or T1D. In addition, we are advancing multiple programs leveraging *in vivo* editing approaches, initially for the treatment and prevention of cardiovascular disease.

Hemoglobinopathies

Our lead product candidate, exa-cel, is an investigational, autologous, *ex vivo* CRISPR gene-edited hematopoietic stem cell therapy that is being evaluated for the treatment of TDT and SCD. Exa-cel is being developed under a joint development and commercialization agreement between us and Vertex Pharmaceuticals Incorporated and certain of its subsidiaries, or Vertex. We and Vertex are investigating exa-cel in two ongoing Phase 1/2/3 open-label clinical trials that are designed to assess the safety and efficacy of a single dose of exa-cel in patients ages 12 to 35 with TDT (CLIMB-111) or SCD (CLIMB-121), respectively. Enrollment is complete for both CLIMB-111 and CLIMB-121. We and Vertex have also initiated two additional Phase 3 open-label clinical trials of exa-cel in pediatric patients with TDT (CLIMB-141) and SCD (CLIMB-151). Patients who received exa-cel in CLIMB-111, CLIMB-121, CLIMB-141 or CLIMB-151 will be asked to participate in a long-term, open-label follow-up trial, CLIMB-131, to evaluate the safety and efficacy of exa-cel. CLIMB-131 is designed to follow participants for up to 15 years after exa-cel infusion. In the second and fourth quarters of 2022, at the European Hematology Association Congress and American Society of Hematology Annual Meeting, respectively, we presented updated clinical data from CLIMB-111 and CLIMB-121 for 44 patients with TDT and 31 patients with SCD treated with exa-cel.

Exa-cel has been granted a number of regulatory designations from the U.S. Food and Drug Administration, or FDA, specifically RMAT, Fast Track, Orphan Drug, and Rare Pediatric Disease designations for the treatment of both TDT and SCD. Exa-cel has also been granted Orphan Drug Designation from the European Commission, as well as PRIME designation from the European Medicines Agency, or EMA, for the treatment of both TDT and SCD. In December 2022, we and Vertex completed regulatory submissions for exa-cel with the EMA and MHRA in the EU and the UK, respectively, and both the EMA and the MHRA have validated the MAA, respectively. In addition, we and Vertex initiated the rolling submission of our BLA in the United States in November 2022 and expect to complete the submission by the end of the first quarter of 2023.

Finally, building upon exa-cel, we have next-generation efforts in targeted conditioning and *in vivo* editing of hematopoietic stem cells, either of which could broaden the number of patients that can benefit from our therapies.

Immuno-Oncology

We believe CRISPR/Cas9 has the potential to create the next generation of CAR T cell therapies that may have a superior product profile compared to current autologous therapies and allow accessibility to broader patient populations. Drawing from the *ex vivo* gene editing capabilities gained through our lead programs, we are advancing several immuno-oncology cell therapy programs, including allogeneic CAR T programs targeting CD19 and CD70.

CD19 Franchise

CTX110, our lead immuno-oncology product candidate, is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting CD19. We are investigating CTX110 in our CARBON clinical trials, which are designed to assess the safety and efficacy of CTX110 in adult patients with relapsed or refractory CD19-positive B-cell malignancies who have received at least two prior lines of therapy. CTX110 has been granted RMAT designation by the FDA.

The Phase 1 CARBON clinical trial is being conducted in two parts – Part A and Part B. In Phase 1 Part A, patients were infused with a single dose of CTX110 across escalating dose levels following a standard lymphodepletion regimen, with an option to re-dose CTX110 based on clinical benefit. In Phase 1 Part B, patients received CTX110 at Dose Level (DL) 4 following standard lymphodepletion, as well as a consolidation dose of CTX110 at the same dose level between four and eight weeks after the initial dose for patients that demonstrated clinical benefit.

In the fourth quarter of 2022, we presented updated clinical data from Phase 1 Part A for 32 patients treated with CTX110, which showed the potential for CTX110 to achieve long-term durable complete remissions, or CRs, with a positively differentiated safety profile in heavily pre-treated patients, and described emerging data from Phase 1 Part B, which showed an encouraging efficacy profile with the potential to improve efficacy with the use of a consolidation dose. Based on this emerging data from our Phase 1 CARBON clinical trial and discussions with regulatory agencies, we have expanded CARBON to include a Phase 2, potentially registrational, single-arm, multi-center, open-label clinical trial that incorporates consolidation dosing. We have begun dosing patients in this pivotal arm.

In parallel with CTX110, we are advancing CTX112, a next-generation investigational, allogeneic CAR T product candidate targeting CD19. CTX112 incorporates additional edits designed to enhance CAR T potency and reducing CAR T exhaustion; and in the fourth quarter of 2022, the IND for CTX112 was cleared by the FDA.

CD70 Franchise

CTX130 is a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting CD70, an antigen expressed on various solid tumors and hematologic malignancies. CTX130 is being investigated in two ongoing independent Phase 1, single-arm, multi-center, open-label clinical trials, COBALT, that are designed to assess the safety and efficacy of several dose levels of CTX130 in adult patients. The COBALT-LYM trial is evaluating the safety and efficacy of CTX130 for the treatment of relapsed or refractory T or B cell malignancies. The COBALT-RCC trial is evaluating the safety and efficacy of CTX130 for the treatment of relapsed or refractory clear cell renal cell carcinoma. CTX130 has received Orphan Drug Designation from the FDA for the treatment of T cell lymphoma and RMAT designation for the treatment of Mycosis Fungoides and Sézary Syndrome (MF/SS), subtypes of Cutaneous T cell Lymphoma (CTCL). In the second quarter of 2022, at the European Hematology Association Congress, we released initial clinical data from the ongoing COBALT-LYM trial for 18 patients with T cell lymphoma treated with CTX130 who had reached at least 28 days of follow-up. Also, in the fourth quarter of 2022, at the Society of Immuno-therapy in Cancer Annual Meeting, we released initial clinical data from the COBALT-RCC trial for 14 patients.

In parallel with CTX130, we are advancing CTX131, a next-generation investigational allogeneic CAR T product candidate targeting CD70 for the potential treatment of both solid tumors and certain hematologic malignancies. CTX131 incorporates additional edits designed to enhance CAR T potency and reducing CAR T exhaustion; and in the first quarter of 2023, the IND for CTX131 was cleared by the FDA.

Additional candidates. Our CRISPR/Cas9 platform enables us to innovate continuously by incorporating incremental edits into next-generation products. In addition to CTX112 and CTX131, we are advancing several additional investigational CAR T product candidates. In addition, as we previously disclosed, following our June 2022 disclosure of high-level data from our Phase 1 clinical trial investigating CTX120, a healthy donor-derived gene-edited allogeneic CAR T investigational therapy targeting B-cell maturation antigen, or BCMA, for the treatment of relapsed or refractory multiple myeloma, we announced plans to pivot to a next-generation investigational allogeneic CAR T targeting BCMA, CTX121, which incorporates proprietary edits to enhance the potency of the CAR T cells and reducing CAR T exhaustion.

Regenerative Medicine

Regenerative medicine, or the use of stem cells to repair or replace tissue or organ function lost due to disease, damage or age, holds the potential to treat both rare and common diseases. Building upon our *ex vivo* gene editing expertise, we have expanded our efforts in this field with a focus on allogeneic stem cell-derived therapies gene edited using CRISPR/Cas9 to enable immune evasion, improve cell function, and direct cell fate. Our first major effort in this area is in diabetes, and we and ViaCyte, Inc., or ViaCyte, which was acquired by Vertex in the third quarter of 2022, are advancing a series of programs as part of a strategic collaboration for the discovery, development, and commercialization of gene-edited stem cell therapies for the treatment of diabetes.

We have a multi-staged product strategy that leverages our CRISPR/Cas9 platform to advance multiple product candidates incorporating incremental edits designed to increase benefit. Our initial product candidate, VCTX210, is an investigational, allogeneic, gene-edited, immune-evasive, stem cell-derived product candidate for the treatment of type 1 diabetes, or T1D, developed by applying our gene editing technology to ViaCyte's proprietary stem cell capabilities. VCTX210 has gene edits designed to promote immune evasion and cell fitness. We and ViaCyte are investigating VCTX210 in an ongoing Phase 1 clinical trial that is designed to assess VCTX210's safety, tolerability, and immune evasion in patients with T1D, and we are in the follow-up stage for this clinical trial. Our next generation product candidate, VCTX211, is an investigational, allogeneic, gene-edited, stem cell-derived product candidate for the treatment of T1D, which incorporates additional gene edits that aim to further enhance cell fitness. In the fourth quarter of 2022, the Clinical Trial Application for VCTX211 was cleared by Health Canada and the Phase 1/2 clinical trial is ongoing.

In Vivo

Our *in vivo* gene editing strategy focuses on gene disruption and whole gene correction – the two technologies required to address the vast majority of the most prevalent severe monogenic diseases. We have established a leading platform for *in vivo* gene disruption, starting in the liver. We plan to advance a broad portfolio of programs across both rare and common diseases with this platform, starting with CVD. Our lead investigational *in vivo* programs, CTX310 and CTX320, target angiopoietin-related protein 3 (ANGPTL3) and lipoprotein(a), respectively, two validated targets for CVD. Gene editing has the potential to shift the treatment paradigm for CVD by recapitulating the proven benefit of natural human genetic variants in a single-dose format. In addition, we continue to develop an expansive whole gene correction platform, starting with using LNPs, and adeno-associated viral vectors, or AAV, in the liver and advancing to AAV-free, HDR-independent methodologies.

CRISPR-X

While we have made significant progress with our current portfolio of programs, we recognize that we need to continue to innovate to unlock the full potential of CRISPR gene editing and bring the potential of transformative therapies to even more patients. In 2022, we launched a new early-stage research team known as CRISPR-X that focuses on innovative research to develop next-

generation editing modalities. CRISPR-X focuses on technologies to enable whole gene correction and insertion without requiring HDR or viral delivery of DNA, such as all-RNA gene correction, non-viral delivery of DNA and novel gene insertion techniques.

Partnerships

Given the numerous potential therapeutic applications for CRISPR/Cas9, we have partnered strategically to broaden the indications we can pursue and accelerate development of programs by accessing specific technologies and/or disease-area expertise. We maintain broad partnerships to develop gene editing-based therapeutics in specific disease areas.

Vertex. We established our initial collaboration agreement in 2015 with Vertex, which focused on TDT, SCD, cystic fibrosis and select additional indications. In December 2017, we entered into a joint development and commercialization agreement with Vertex pursuant to which, among other things, we are co-developing and preparing to co-commercialize exa-cel for TDT and SCD. In April 2021, we and Vertex amended and restated our existing joint development and commercialization agreement, pursuant to which, among other things, we will continue to develop and prepare to commercialize exa-cel for TDT and SCD in partnership with Vertex. We also entered into a strategic collaboration and license agreement with Vertex in June 2019 for the development and commercialization of products for the treatment of Duchenne muscular dystrophy and myotonic dystrophy type 1.

ViaCyte. We entered into a research and collaboration agreement in September 2018 with ViaCyte to pursue the discovery, development and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes, and in July 2021, we entered into a joint development and commercialization agreement with ViaCyte, or the ViaCyte JDCA. In connection with entering into the ViaCyte JDCA, our existing research collaboration agreement with ViaCyte expired in accordance with its terms. Under the ViaCyte JDCA, we and ViaCyte are jointly developing and will commercialize product candidates and shared products for use in the treatment of diabetes type 1, diabetes type 2 and insulin dependent/requiring diabetes, or the ViaCyte Collaboration Field, throughout the world. The ViaCyte JDCA includes, among other things, provisions relating to collaboration and program governance, clinical activities for the product candidates and shared products under the agreement and continuing research by the parties in the ViaCyte Collaboration Field. Unless otherwise mutually agreed, research costs incurred by a party will be solely borne by such party. The program expenses, as originally set forth in the research and collaboration agreement, as applicable, incurred through the date of first commercial sale of a shared product will be allocated 60% to us and 40% to ViaCyte. Following first commercial sale of a shared product, such program expenses will be shared equally between us and ViaCyte. Shared product revenues will be shared equally by us and ViaCyte. In the third quarter of 2022, Vertex announced it had acquired ViaCyte and the rights to the ViaCyte Collaboration Field.

Bayer. We entered into an option agreement in the fourth quarter of 2019 with Bayer pursuant to which Bayer has an option to co-develop and co-commercialize two products that we advance for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders for a specified period of time, or, under certain circumstances, exclusively license such optioned products.

Other Partnerships. We have entered into a number of additional collaborations and license agreements to support and complement our hematopoietic stem cell, immuno-oncology, regenerative medicine and *in vivo* programs and platform, including agreements with: Nkarta, Inc. to co-develop and co-commercialize two donor-derived, gene-edited CAR-NK cell product candidates and a product candidate combining NK and T cells; Capsida Biotherapeutics, Inc. to develop *in vivo* gene editing therapies delivered with engineered AAV vectors for the treatment of amyotrophic lateral sclerosis and Friedreich's ataxia; Moffitt Cancer Center and Roswell Park Comprehensive Cancer Center to advance autologous CAR T programs against new targets; MaxCyte, Inc. on *ex vivo* delivery for our hemoglobinopathy and immuno-oncology programs; CureVac AG on optimized mRNA constructs and manufacturing for certain *in vivo* programs; and KSQ Therapeutics, Inc. on intellectual property for our allogeneic immuno-oncology programs.

For additional information regarding the key terms of these arrangements, please see "*Business—Strategic Partnerships and Collaborations*".

Impacts of Coronavirus and Market Conditions on Our Business

We have been actively monitoring the coronavirus pandemic situation and its impact globally. We believe our financial results for the years ended December 31, 2022, 2021 and 2020 were not significantly impacted by the outbreak of the coronavirus. We believe our hybrid and remote working arrangements have had limited impact on our ability to maintain internal operations during the years ended December 31, 2022, 2021 and 2020. Further, disruption of global financial markets and a recession or market correction, including as a result of the coronavirus pandemic, the ongoing military conflict between Russia and Ukraine and the related sanctions imposed against Russia, and other global macroeconomic factors such as inflation, could reduce our ability to access capital, which could, in the future, negatively affect our business and the value of our common shares.

Financial Overview

Since our inception in October 2013, we have devoted substantially all of our resources to our research and development efforts, undertaking drug discovery and preclinical development activities, building and protecting our intellectual property estate, organizing

and staffing our company, business planning, raising capital and providing general and administrative support for these operations. To date, we have primarily financed our operations through private placements of our preferred shares, common share issuances, convertible loans and collaboration agreements with strategic partners.

While we were in a net income position in certain previous years due to upfronts associated with our collaborations with Vertex, we have a history of recurring losses and expect to continue to incur losses for the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase significantly as we continue our current research programs and development activities; seek to identify additional research programs and additional product candidates; conduct initial drug application supporting preclinical studies and initiate clinical trials for our product candidates; initiate preclinical testing and clinical trials for any other product candidates we identify and develop; maintain, defend, protect and expand our intellectual property estate; further develop our gene editing platform; hire additional research, clinical and scientific personnel; incur facilities costs associated with such personnel growth; develop manufacturing infrastructure and conduct related regulatory validation activities; and incur additional costs associated with operating as a public company.

Revenue Recognition

We have not generated any revenue to date from product sales and do not expect to do so in the near future. During the years ended December 31, 2022, 2021 and 2020, we recognized $0.4 million, $913.1 million and $0.5 million, respectively, of revenue related to our collaboration agreements with Vertex.

For the years ended December 31, 2022, 2021 and 2020, we generated $0.8 million, $1.9 million and $0.2 million, respectively, of grant revenue related to certain contracts with not-for-profit entities.

For additional information about our revenue recognition policy, see Note 2 and Note 8 of the notes to our audited consolidated financial statements included in this Annual Report on Form 10-K.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our product discovery efforts and the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits and equity-based compensation expense;
- costs of services performed by third parties that conduct research and development and preclinical activities on our behalf;
- costs of purchasing lab supplies and non-capital equipment used in our preclinical activities and in manufacturing preclinical and clinical study materials;
- consultant fees;
- facility costs, including rent, depreciation and maintenance expenses; and
- fees and other payments related to acquiring and maintaining licenses under our third-party licensing agreements.

Our external research and development expenses support our various preclinical and clinical programs, and as such we do not break down external research and development expenses further. Our internal research and development expenses consist of payroll and benefits expenses, facilities expense, and other indirect research and development expenses incurred in support of overall research and development activities and as such are not allocated to a specific development stage or therapeutic area. Research and development costs are expensed as incurred. Nonrefundable advance payments for research and development goods or services to be received in the future are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed. At this time, we cannot reasonably estimate or know the nature, timing or estimated costs of the efforts that will be necessary to complete the development of any product candidates we may identify and develop. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty of:

- successful completion of preclinical studies and IND-enabling studies;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity;
- launching commercial sales of the product, if and when approved, whether alone or in collaboration with others;
- acceptance of the product, if and when approved, by patients, the medical community and third-party payors;

- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- achieving desirable medicinal properties for the intended indications.

A change in the outcome of any of these variables with respect to the development of any product candidates or the subsequent commercialization of any product candidates we may successfully develop could significantly change the costs, timing and viability associated with the development of that product candidate.

Research and development activities are central to our business model. We expect our research and development costs to increase significantly for the foreseeable future as our current development programs progress, new programs are added and as we continue to prepare regulatory filings. These increases will likely include the costs related to the implementation and expansion of clinical trial sites and related patient enrollment, monitoring, program management and manufacturing expenses for current and future clinical trials.

General and Administrative Expenses

General and administrative expenses consist primarily of employee related expenses, including salaries, benefits and equity-based compensation, for personnel in executive, finance, accounting, business development and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

We expect to continue to incur general and administrative expenses consistent with research and development at companies of our size and stage of development, which may increase in the future to support continued research and development activities, and potential commercialization of our product candidates. In addition, we anticipate ongoing expenses related to the reimbursements of third-party patent related expenses in connection with certain of our in-licensed intellectual property.

Collaboration Expense, Net

Collaboration expense, net, consists of operating expenses related to exa-cel under our collaboration with Vertex. The A&R Vertex JDCA allows us to defer a portion of our share of costs under the arrangement if spending on the exa-cel program exceeds specified amounts. Any deferred amounts are only payable to Vertex as an offset against future profitability of the exa-cel program and the amounts payable are capped at a specified maximum amount per year.

Other Income

Other income consists primarily of interest income earned on investments.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles. We believe that several accounting policies are important to understanding our historical and future performance. We refer to these policies as critical because these specific areas generally require us to make judgments and estimates about matters that are uncertain at the time we make the estimate, and different estimates—which also would have been reasonable—could have been used. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and other market-specific or other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

Revenue

Accounting Standards Codification Topic 606, *Revenue from Contracts with Customers*, or ASC 606, applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases and collaboration arrangements. To

determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps:

1) Identify the contract with the customer

A contract with a customer exists when (i) we enter into an enforceable contract with a customer that defines each party's rights regarding the goods or services to be transferred and identifies the related payment terms, (ii) the contract has commercial substance and (iii) we determine that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

2) Identify the performance obligations in the contract

Performance obligations promised in a contract are identified based on the goods and services that will be transferred to the customer that are both capable of being distinct, whereby the customer can benefit from the good or service either on its own or together with other available resources, and are distinct in the context of the contract, whereby the transfer of the good or service is separately identifiable from other promises in the contract. To the extent a contract includes multiple promised goods and services, we must apply judgment to determine whether promised goods and services are capable of being distinct and distinct in the context of the contract. If these criteria are not met, the promised goods and services are accounted for as a combined performance obligation.

3) Determine the transaction price

The transaction price is determined based on the consideration to which we will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, such as research, development, regulatory and commercial milestones, we determine if it is probable that we will receive such amounts and there is no risk of a significant revenue reversal. When we cannot conclude that receipt of such amounts is probable, we constrain the related variable consideration resulting in its exclusion from transaction consideration. In determining the portion of the transaction consideration to be constrained, we consider the probability and uncertainty that the related research, developmental, regulatory and commercial milestones will be achieved given the nature of research and clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, we consider both internal and external information available, including information from industry publications and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

4) Allocate the transaction consideration to performance obligations in the contract

If the contract contains a single performance obligation, the entire transaction consideration is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction consideration to each performance obligation on a relative standalone selling price basis unless the transaction consideration is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. In determining these estimated standalone selling prices, we make a number of significant judgements including, for licenses, management's assumptions regarding probability weighted projected discounted cash flows for each of the collaboration development programs. The estimated standalone selling prices are sensitive to changes in assumptions, such as probabilities of scientific success, discount rate and certain assumptions that form the basis of forecasted cash flows. In developing these assumptions, management considers both internal and external information available, including information from other guideline companies within the same industry and other relevant factors. Changes to these assumptions can have a material effect on the allocation of the transaction consideration to performance obligations, as well as the amount and timing of revenue recognized.

5) Recognize revenue when or as we satisfy a performance obligation

We satisfy performance obligations over time or at a point in time, depending on the nature of the performance obligation. Revenue is recognized over time if the customer simultaneously receives and consumes the benefits provided by the entity's performance, the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or the entity's performance does not create an asset with an alternative use to the entity and the entity has an enforceable right to payment for performance completed to date. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

Collaboration Arrangements

We record the elements of our collaboration agreements that represent joint operating activities in accordance with ASC 808, *Collaborative Arrangements*, or ASC 808. Accordingly, the elements of the collaboration agreements that represent activities in which both parties are active participants and to which both parties are exposed to the significant risks and rewards that are dependent on the commercial success of the activities, are recorded as collaborative arrangements.

We evaluate the proper presentation of the commercial activities and the profit and loss sharing associated with the collaboration agreements. ASC 808 states that when payments between parties in a collaborative arrangement are not within the scope of other authoritative accounting literature, the income statement classification should be based on the nature of the arrangement, the nature of its business operations and the contractual terms of the arrangement. To the extent that these payments are not within the scope of other authoritative accounting literature, the income statement classification for the payments shall be based on an analogy to authoritative accounting literature or if there is no appropriate analogy, a reasonable, rational, and consistently applied accounting policy election.

Accrued research and development expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to development, manufacturing and distribution of clinical trial materials.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period and adjust accordingly.

Equity-Based Compensation

Our share-based compensation programs grant awards that have included stock options, restricted stock units and restricted stock awards. Grants are awarded to employees and non-employees, including directors.

We account for our stock-based compensation awards in accordance with ASC Topic 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees and non-employee directors, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. We use the Black-Scholes option pricing model to determine the fair value of options granted.

We account for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Our stock-based awards are subject to service or performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

We expense restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award.

We estimate the fair value of our option awards to employees, directors and non-employees using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of complete company-specific historical and implied volatility data for the full expected term of the stock-based awards, we base our estimate of expected volatility on a representative group of publicly traded companies in addition to our own volatility data. For these analyses, we selected

companies with comparable characteristics to our own, including enterprise value, risk profiles, position within the industry and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We have estimated the expected term of our employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. We have never paid, and do not expect to pay, dividends in the foreseeable future.

Recent Accounting Pronouncements

Refer to Note 2 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for a discussion of recent accounting pronouncements.

Results of Operations

The following is a discussion of the components of results of operations. This section generally discusses 2022 and 2021 items and year-to-year comparisons between 2022 and 2021. Discussions of 2020 items and year-to-year comparisons between 2021 and 2020 that are not included in this Annual Report on Form 10-K can be found in "Management's Discussion and Analysis of Financial Condition and Results of Operations" Part II, Item 7 of our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 filed on February 15, 2022.

Comparison of Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021, together with the dollar change in those items:

	Years Ended December 31,		Period to Period Change
	2022	2021	
		(in thousands)	
Revenue:			
Collaboration revenue	$ 436	$ 913,081	$ (912,645)
Grant revenue	762	1,882	(1,120)
Total revenue	1,198	914,963	(913,765)
Operating expenses:			
Research and development	461,645	340,567	121,078
General and administrative	102,464	99,690	2,774
Collaboration expense, net	110,250	101,178	9,072
Total operating expenses	674,359	541,435	132,924
(Loss) income from operations	(673,161)	373,528	(1,046,689)
Other income, net	22,661	6,003	16,658
Net (loss) income before income taxes	(650,500)	379,531	(1,030,031)
Benefit (provision) for income taxes	325	(1,870)	2,195
Net (loss) income	$ (650,175)	$ 377,661	$ (1,027,836)

Collaboration Revenue

Collaboration revenue was $0.4 million for the year ended December 31, 2022, compared to $913.1 million for the year ended December 31, 2021. Collaboration revenue for the year ended December 31, 2021 was primarily associated with the $900.0 million upfront payment from Vertex in connection with the A&R Vertex JDCA, as well as the achievement of a $12.5 million milestone under the 2019 Collaboration Agreement with Vertex, of which $12.0 million was recorded as revenue in 2021. Refer to Note 8 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for a description of revenue recognized related to Vertex.

Grant Revenue

Grant revenue was $0.8 million and $1.9 million, respectively, for the years ended December 31, 2022 and 2021.

Research and Development Expenses

Research and development expenses were $461.6 million for the year ended December 31, 2022, compared to $340.6 million for the year ended December 31, 2021. The following table summarizes our research and development expenses for the years ended December 31, 2022 and 2021, together with the changes in those items in dollars (in thousands):

	Years Ended December 31,		Period to Period
	2022	2021	Change
External research and development expenses	$ 197,742	$ 118,698	$ 79,044
Employee related expenses	81,683	53,100	28,583
Facility expenses	114,591	99,252	15,339
Stock-based compensation expenses	53,956	59,683	(5,727)
Other expenses	2,864	2,016	848
Sublicense and license fees	10,809	7,818	2,991
Total research and development expenses	$ 461,645	$ 340,567	$ 121,078

The increase of approximately $121.1 million was primarily attributable to the following:

- $79.0 million of increased external research and development costs, primarily associated with production of drug product and increased clinical trial expense associated with our immuno-oncology programs;
- $28.6 million of increased employee-related expenses primarily due to reallocation of resources from the exa-cel program, which are presented within "collaboration expense, net" in the consolidated statements of operations and comprehensive (loss) income, to our wholly-owned programs; and
- $15.3 million of increased facility expenses due to the opening of our U.S. headquarters for research and development in Boston, MA.

General and Administrative Expenses

General and administrative expenses were $102.5 million for the year ended December 31, 2022, compared to $99.7 million for the year ended December 31, 2021. The increase of $2.8 million was primarily attributable to increased employee compensation, benefit and other headcount-related expenses.

Collaboration Expense, net

Collaboration expense, net, was $110.3 million for the year ended December 31, 2022, compared to $101.2 million for the year ended December 31, 2021. The increase of approximately $9.1 million was primarily attributable to increased manufacturing and other pre-commercial costs.

Under the A&R Vertex JDCA, we have an option to defer our portion of specified costs on the exa-cel program in excess of $110.3 million for the years ended December 31, 2022, 2023 and 2024. Vertex may only recover any such deferred amounts as an offset against future profitability of the exa-cel program, determined on an annual basis in accordance with the A&R Vertex JDCA. Any such deferred amounts are capped at a specified maximum amount per year.

For the year ended December 31, 2022, we exercised our option to defer $36.1 million of our share of costs incurred under the A&R Vertex JDCA. These deferred costs will be recognized by us when recoverability of such deferred amounts by Vertex is probable and the amount can be reasonably estimated. As of December 31, 2022, no such deferred amounts have been recognized.

Other Income, net

Other income, net, was $22.7 million for the year ended December 31, 2022, compared to $6.0 million for the year ended December 31, 2021. Other income, net, for the year ended December 31, 2022 consisted primarily of interest income earned on cash, cash equivalents and marketable securities during the year.

Liquidity and Capital Resources

Sources of Liquidity

As of December 31, 2022, we had cash, cash equivalents and marketable securities of approximately $1,868.4 million, of which $5.1 million was held outside of the United States.

With our cash on hand as of December 31, 2022, we expect cash, cash equivalents and marketable securities to be sufficient to fund our current operating plan through at least the next 24 months.

We have predominantly incurred losses and cumulative negative cash flows from operations since our inception, and as of December 31, 2022, we had an accumulated deficit of $846.1 million. We anticipate that we will continue to incur losses for at least the next several years. We expect to continue to incur operating expenses consistent with research and development at companies of our size and stage of development, which may increase in the future to support continued research and development activities, and potential commercialization of our product candidates.

Since our initial public offering, we have primarily financed our operations through common share issuances and collaboration agreements with strategic partners. Recent sources of equity financing include:

Public Offerings

In July 2020, we sold 7.4 million common shares through an underwritten public offering (inclusive of shares sold pursuant to the exercise of the underwriters' option to purchase additional shares) at a public offering price of $70.00 per share for aggregate net proceeds of $489.7 million, which were net of equity issuance costs of $27.6 million. Additional equity issuance costs of $4.9 million for stamp taxes were accrued as of December 31, 2020 and paid in 2021.

At-the-Market Offerings

- In August 2019, we entered into an Open Market Sale Agreement[SM] with Jefferies under which we are able to offer and sell, from time to time at our sole discretion through Jefferies, as our sales agent, our common shares, par value of CHF 0.03 per share, or the August 2019 Sales Agreement. In August 2019, in connection with the August 2019 Sales Agreement, we filed a prospectus supplement with the SEC to offer and sell, from time to time, common shares having aggregate gross proceeds of up to $200.0 million, or the 2019 ATM. In connection with our entry into the August 2019 Sales Agreement, our August 2018 Open Market Sale Agreement[SM] with Jefferies was mutually terminated by us and Jefferies. During the year ended December 31, 2020, we issued and sold an aggregate of 2.2 million common shares under the 2019 ATM at an average price of $89.47 per share for aggregate proceeds of $195.5 million, which were net of equity issuance costs of $4.5 million.
- In December 2020, in connection with the August 2019 Sales Agreement, we filed a prospectus supplement with the SEC to offer and sell from time to time common shares having aggregate gross proceeds of up to $350.0 million, or the 2020 ATM. During the year ended December 31, 2020, we issued and sold an aggregate of 1.8 million common shares under the 2020 ATM at an average price of $169.57 per share for aggregate proceeds of $298.0 million, which were net of equity issuance costs of $4.5 million. Additional equity issuance costs for stamp taxes related to shares sold in 2020 related to the 2019 and 2020 ATM were $4.9 million, of which $4.0 million was accrued as of December 31, 2020 and paid in 2021.
- In January 2021, we issued and sold under the 2020 ATM an aggregate of 0.3 million common shares at an average price of $162.46 per share with aggregate proceeds of $46.7 million, which were net of equity issuance costs of $0.7 million. An additional $0.5 million of stamp taxes on this amount was paid in 2021.
- In January 2021, in connection with the August 2019 Sales Agreement, we filed a prospectus supplement with the SEC to offer and sell from time to time common shares having aggregate gross proceeds of up to $600.0 million. In July 2021, we filed a new prospectus supplement with the SEC, which replaced the previous prospectus supplement filed in January 2021, to offer and sell, from time to time, the common shares remaining under the original prospectus supplement having aggregate gross proceeds of up to $419.8 million, or, together with the January 2021 prospectus supplement, the 2021 ATM. As of December 31, 2022, we have issued and sold an aggregate of 1.1 million common shares under the 2021 ATM at an average price of $168.79 per share for aggregate proceeds of $178.8 million, which were net of equity issuance costs of $2.4 million.

Sources of Liquidity

Cash Flows

Discussions of 2020 items and year-to-year comparisons between 2021 and 2020 that are not included in this Annual Report on Form 10-K can be found in "Management's Discussion and Analysis of Financial Condition and Results of Operations" Part II, Item 7 of our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 filed on February 15, 2022.

The following table provides information regarding our cash flows for each of the periods below:

	Years Ended December 31,	
	2022	2021
	(in thousands)	
Net cash (used in) provided by operating activities	$ (495,741)	$ 538,972
Net cash used in investing activities	(258,655)	(1,035,430)
Net cash provided by financing activities	38,592	250,945
Effect of exchange rate changes on cash	(80)	(11)
(Decrease) increase in cash and restricted cash	$ (715,884)	$ (245,524)

Operating Activities

Net cash used in operating activities was $495.7 million for the year ended December 31, 2022, compared to cash provided by operating activities of $539.0 million for the year ended December 31, 2021. The increase in cash used in operating activities was primarily driven by an increase in net loss of $1,027.8 million, from net income of $377.7 million for the year ended December 31, 2021 to net loss of $650.2 million for the year ended December 31, 2022, as well as a $7.0 million decrease in net changes of operating assets and liabilities.

Investing Activities

Net cash used in investing activities for the year ended December 31, 2022 was $258.7 million and consisted of purchases of marketable securities, net of maturities, of $221.5 million, as well as $37.2 million in purchases of property and equipment for use in research and development activities.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022 was $38.6 million and consisted of net proceeds of $37.6 million from stock option exercises and ESPP contributions.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, research and development activities, manufacturing activities, compensation and related expenses, laboratory and related supplies, legal and other regulatory expenses, patent prosecution filing, defense and intellectual property maintenance costs, and general overhead costs, including costs associated with operating as a public company. We expect to continue to incur operating expenses consistent with research and development at companies of our size and stage of development, which may increase in the future to support continued research and development activities, and potential commercialization of our product candidates.

Because most of our programs are still in early stages of development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development, manufacture and commercialization of any current or future product candidates, if approved, or whether, or when, we may achieve profitability. Until such time as we can generate substantial product revenues, if ever, we expect to finance our cash needs through a combination of equity financings, debt financings and payments received in connection with our collaboration agreements. We intend to consider opportunities to raise additional funds through the sale of equity or debt securities when market conditions are favorable to us to do so. However, the trading prices for our common shares and other biopharmaceutical companies have been highly volatile. As a result, we may face difficulties raising capital through sales of our common shares or such sales may be on unfavorable terms. In addition, a recession, depression or other sustained adverse market event, including resulting from the continued spread of the coronavirus, could materially and adversely affect our business and the value of our common shares. To the extent that we raise additional capital through the future sale of equity or debt securities, the ownership interests of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing shareholders. If we raise additional funds through collaboration arrangements in the future, 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.

Outlook

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditures for at least the next 24 months without giving effect to any additional proceeds we may receive under our collaboration with Vertex and any other capital raising transactions we may complete. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Given our need for additional financing to support the long-term clinical development of our programs, we intend to consider additional financing opportunities when market terms are favorable to us.

Our ability to generate revenue and achieve profitability depends significantly on our success in many areas, including: developing our delivery technologies and our gene editing technology platform; selecting appropriate product candidates to develop; completing research and preclinical and clinical development of selected product candidates; obtaining regulatory approvals and marketing authorizations for product candidates for which we complete clinical trials; developing a sustainable and scalable manufacturing process for product candidates; launching and commercializing product candidates for which we obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor; obtaining market acceptance of our product candidates, if approved; addressing any competing technological and market developments; negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter; maintaining good relationships with our collaborators and licensors; maintaining, defending, protecting and expanding our estate of intellectual property rights, including patents, trade secrets and know-how; and attracting, hiring and retaining qualified personnel.

Contractual and Other Obligations

Operating lease and sublease obligations

Our operating lease obligations primarily consist of lease payments on our office and laboratory facility in Boston, Massachusetts, as well as lease payments on our cell manufacturing facility in Framingham, Massachusetts, which are described in further detail in Note 7 of our consolidated financial statements included in this Annual Report on Form 10-K. Future contractual payments on operating lease and sublease obligations due within one year of December 31, 2022 are $29.3 million, and future contractual payments on operating lease and sublease obligations due greater than one year from December 31, 2022 are $310.9 million.

Other obligations

Under the Invention Management Agreement signed on December 15, 2016, we are obligated to share costs related to patent maintenance, defense and prosecution for the CRISPR/Cas9 gene editing intellectual property with California, Vienna and their licensees including Caribou, and Caribou's licensee Intellia Therapeutics. Such costs are not quantifiable at this time.

Under the A&R Vertex JDCA, we are allowed to defer a portion of our share of costs under the arrangement if spending on the exa-cel program exceeds specified amounts. Any deferred amounts are only payable to Vertex as an offset against future profitability of the exa-cel program and the amounts payable are capped at a specified maximum amount per year. Deferred costs associated with the exa-cel program have not been accrued as of December 31, 2022 because a reasonable estimate of future payments against future profitability cannot be made.

In the normal course of business, we enter into agreements with contract research organizations for clinical trials and clinical supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. These contracts are generally cancelable at any time by us upon less than 180 days' prior written notice. Certain of these agreements require us to pay milestones to such third parties upon achievement of certain development, regulatory or commercial milestones as further described in Note 9 of our consolidated financial statements included in this Annual Report on Form 10-K. Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent on the successful achievement of certain development, regulatory approval and commercial milestones, which may not be achieved.

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain milestones, including future payments to third parties with whom we have entered into research, development and commercialization agreements. We have not included these commitments on our balance sheet because the achievement and timing of these milestones is not fixed and determinable.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Sensitivity

We are exposed to market risk related to changes in interest rates. As of December 31, 2022, we had cash, cash equivalents and marketable securities of $1,868.4 million, primarily invested in U.S. treasury securities and government agency securities, corporate bonds, commercial paper and money market accounts invested in U.S. government agency securities. Due to the conservative nature of these instruments, we do not believe that we have a material exposure to interest rate risk. If interest rates were to increase or decrease by 1%, the fair value of our investment portfolio would increase or decrease by an immaterial amount.

Foreign Currency Exchange Rate Risk

As a result of our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Swiss Franc and British Pound, against the U.S. dollar. The current exposures arise primarily from cash, accounts payable and intercompany receivables and payables. Changes in foreign exchange rates affect our consolidated statement of operations and distort comparisons between periods. To date, foreign currency transaction gains and losses have not been material to our financial statements, and we have not engaged in any foreign currency hedging transactions.

Inflation

Inflation generally affects us by increasing our cost of labor, clinical trial and manufacturing costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2022, 2021 and 2020.

Item 8. Financial Statements and Supplementary Data.

The consolidated financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

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 chief executive officer and chief financial officer, after evaluating the effectiveness of our disclosure controls and procedures (as defined in Rule 13a-15(e) and Rule 15d-15(e) promulgated under the Securities Exchange Act of 1934, as amended) as of the end of the period covered by this Annual Report on Form 10-K, have concluded that, based on such evaluation, our disclosure controls and procedures were effective. In designing and evaluating the disclosure controls and procedures, our management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and Rule 15d-15(f) promulgated under the Securities Exchange Act of 1934, as amended, as a process designed by, or under the supervision of, our principal executive and principal financial officers 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. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of the assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- 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.

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.

Our management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2022. In making this assessment, it used the criteria set forth in the Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework)(COSO). Based on its assessment, our management has concluded that, as of December 31, 2022, the Company's internal control over financial reporting is effective based on those criteria.

Our independent registered public accounting firm, Ernst & Young LLP, issued an attestation report on our internal control over financial reporting. See below.

Changes in Internal Control Over Financial Reporting

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, during the fourth quarter of 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and the Board of Directors of CRISPR Therapeutics AG

Opinion on Internal Control Over Financial Reporting

We have audited CRISPR Therapeutics AG's internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, CRISPR Therapeutics AG (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2022 and 2021 the related consolidated statements of operations and comprehensive (loss) income, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2022, and the related notes and our report dated February 21, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible 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 internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

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.

/s/ Ernst & Young LLP

Boston, Massachusetts

February 21, 2023

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item is incorporated by reference to our Proxy Statement for our 2023 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022.

Item 11. Executive Compensation.

The information required by this item is incorporated by reference to our Proxy Statement for our 2023 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2023 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022.

Item 14. Principal Accountant Fees and Services.

The information required by this item is incorporated by reference to our Proxy Statement for our 2023 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2022.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a)(1) Financial Statements.

See the "*Index to Consolidated Financial Statements*" on page F-1 below for the list of financial statements filed as part of this report.

Schedules other than that listed above have been omitted because of the absence of conditions under which they are required or because the required information is included in the financial statements or the notes thereto.

(a)(2) Exhibits.

The exhibits listed in the Exhibit Index below are filed or incorporated by reference as part of this Annual Report on Form 10-K.

Exhibit Index

Exhibit Number	Description
3.1	Amended and Restated Articles of Association of CRISPR Therapeutics AG, dated June 9, 2022 (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on June 13, 2022).
4.1*	Description of Capital Shares
10.1†	License Agreement, dated April 15, 2014, by and between CRISPR Therapeutics AG and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.5 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.2†	License Agreement, dated April 15, 2014, by and between TRACR Hematology Limited and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.6 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.3†	Patent Assignment Agreement, dated November 7, 2014, by and between CRISPR Therapeutics AG, Emmanuelle Marie Charpentier, the University of Vienna and Ines Fonfara (incorporated herein by reference to Exhibit 10.7 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.4	Form of Indemnification Agreement (incorporated herein by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.5#	Employment Agreement, dated December 1, 2017, by and between CRISPR Therapeutics AG and Rodger Novak (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 21, 2017).
10.6#	Mandate Agreement, dated December 27, 2019, by and between CRISPR Therapeutics AG and Oriolus Consulting LLC (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 27, 2019).
10.7#	Termination Agreement, dated December 27, 2019, by and between CRISPR Therapeutics AG and Rodger Novak (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 27, 2019).

10.8#	Second Amended and Restated Employment Agreement, dated October 2, 2017, by and between CRISPR Therapeutics, Inc. and Samarth Kulkarni (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on October 2, 2017).
10.9#	Employment Agreement, dated May 31, 2017, by and between CRISPR Therapeutics, Inc. and James R. Kasinger (incorporated herein by reference to Exhibit 10.16 to the Company's Annual Report on Form 10-K filed on March 8, 2018).
10.10#	Employment Agreement, dated January 2, 2019, by and between CRISPR Therapeutics, Inc. and Lawrence Klein (incorporated herein by reference to Exhibit 10.16 to the Company's Annual Report on Form 10-K filed on February 25, 2019).
10.11#	Employment Agreement, dated October 14, 2021, by and between CRISPR Therapeutics, Inc. and Brendan Smith (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on October 14, 2021).
10.12#	Employment Agreement, dated May 23, 2022, by and between CRISPR Therapeutics AG and Phuong Khanh Morrow (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on August 8, 2022).
10.13#	Senior Executive Cash Incentive Bonus Plan (incorporated herein by reference to Exhibit 10.26 to the Company's Annual Report on Form 10-K filed on March 8, 2018).
10.14#	CRISPR Therapeutics AG 2015 Stock Option and Grant Plan (incorporated herein by reference to Exhibit 10.14 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.15#	CRISPR Therapeutics AG Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on June 2, 2017).
10.15.1#	Form of Incentive Stock Option Agreement under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.15.2#	Form of Non-Qualified Stock Option Agreement for Company Employees under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.3 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.15.3#	Form of Non-Qualified Stock Option Agreement for Non-Employee Directors under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.4 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.15.4#	Form of Restricted Stock Award Agreement under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.5 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.15.5#	Form of Restricted Stock Award Agreement for Company Employees under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.6 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.15.6#	Form of Restricted Stock Award Agreement for Non-Employee Directors under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.7 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.16#	CRISPR Therapeutics AG 2018 Stock Option and Incentive Plan and forms of agreements thereunder (incorporated herein by reference to Exhibit 99.1 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.16.1#	Form of Incentive Stock Option Agreement under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.2 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.16.2#	Form of Non-Qualified Stock Option Agreement for Company Employees under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.3 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).

10.16.3#	Form of Non-Qualified Stock Option Agreement for Non-Employee Directors under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.4 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.16.4#	Form of Restricted Stock Award under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.5 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.16.5#	Form of Restricted Stock Award Agreement for Company Employees under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.6 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.16.6#	Form of Restricted Stock Award for Non-Employee Directors under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.7 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.17#	Amendment No. 1 to the 2018 Stock Option and Incentive Plan (incorporated herein by reference to Appendix A to the Company's Definitive Proxy Statement on Schedule 14A filed on April 30, 2019).
10.18#	Amendment No. 2 to the 2018 Stock Option and Incentive Plan (incorporated herein by reference to Appendix A to the Company's Definitive Proxy Statement on Schedule 14A filed on April 24, 2020).
10.19#	Amendment No. 3 to the 2018 Stock Option and Incentive Plan (incorporated herein by reference to Appendix A to the Company's Definitive Proxy Statement on Schedule 14A filed on April 25, 2022).
10.20#	CRISPR Therapeutics AG 2016 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.16 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.21†	Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement for a Programmable DNA Restriction Enzyme for Genome Editing, dated December 15, 2016, by and among CRISPR Therapeutics AG, The Regents of the University of California, University of Vienna, Dr. Emmanuelle Charpentier, Intellia Therapeutics, Inc., Caribou Biosciences, Inc., ERS Genomics Ltd., and TRACR Hematology Ltd. (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 16, 2016).
10.22†	Strategic Collaboration, Option and License Agreement, dated October 26, 2015, by and among CRISPR Therapeutics AG, CRISPR Therapeutics Limited, CRISPR Therapeutics, Inc., TRACR Hematology Limited, Vertex Pharmaceuticals, Incorporated and Vertex Pharmaceuticals (Europe) Limited (incorporated herein by reference to Exhibit 10.4 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.23†	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement by and between, on the one hand, Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited, and on the other hand, CRISPR Therapeutics AG, CRISPR Therapeutics, Inc., CRISPR Therapeutics Limited and TRACR Hematology Ltd., dated as of December 12, 2017 (incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 18, 2017).
10.24†	Amendment No. 2 to the Strategic Collaboration, Option and License Agreement by and between, on the one hand, Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited, and on the other hand, CRISPR Therapeutics AG, CRISPR Therapeutics, Inc., CRISPR Therapeutics Limited and TRACR Hematology Ltd., dated as of June 6, 2019 (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on July 29, 2019).
10.25†	Strategic Collaboration and License Agreement dated June 6, 2019, between CRISPR Therapeutics AG and Vertex Pharmaceuticals Incorporated (incorporated herein by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on July 29, 2019).
10.26†	First Amendment to the Strategic Collaboration and License Agreement dated March 17, 2021, between CRISPR Therapeutics AG and Vertex Pharmaceuticals Incorporated (incorporated herein by reference to Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q filed on April 27, 2021).
10.27†^	Amended and Restated Joint Development and Commercialization Agreement between, on the one hand, Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited, and on the other hand, CRISPR Therapeutics AG, CRISPR Therapeutics Limited, CRISPR Therapeutics, Inc., and TRACR Hematology Ltd., dated as of April 16, 2021 (incorporated herein by reference to Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q filed on April 27, 2021).

10.28†	Option Agreement, dated December 13, 2019, between CRISPR Therapeutics AG and Bayer HealthCare LLC (incorporated herein by reference to Exhibit 10.31 to the Company's Annual Report on Form 10-K filed on February 12, 2020).
10.29^	Lease, dated May 5, 2020, by and between CRISPR Therapeutics, Inc. and CRP/KING 33 NY AVE. OWNER, L.L.C. (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on April 27, 2021).
10.30^	First Amendment to Lease dated December 2, 2020, by and between CRISPR Therapeutics, Inc. and CRP/KING 33 NY AVE. OWNER, L.L.C. (incorporated herein by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on April 27, 2021).
10.31^	Second Amendment to Lease dated April __, 2021, by and between CRISPR Therapeutics, Inc. and 33 NYA OWNER (DE) LLC, as successor in interest to CRP/KING 33 NY AVE. OWNER, L.L.C. (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on July 29, 2021).
10.32†	Lease, dated July 24, 2020, by and between CRISPR Therapeutics, Inc. and 105 W First Street Owner, L.L.C. (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on July 27, 2020).
10.33	Letter Agreement dated January 6, 2022, by and between CRISPR Therapeutics, Inc. and 105 W First Street Owner, L.L.C. (incorporated herein by reference to Exhibit 10.37 to the Company's Annual Report on Form 10-K filed on February 15, 2022).
10.34	Lease Commencement Date Agreement, dated May 1, 2022, by and between CRISPR Therapeutics AG and 105 W First Street Owner, L.L.C. (incorporated herein by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on August 8, 2022).
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Ernst & Young LLP
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
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.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

* Filed herewith.

+ Furnished herewith.

† Certain portions of this exhibit have been omitted because they are not material and the registrant customarily and actually treats that information as private or confidential.

A management contract or compensatory plan or arrangement required to be filed as an exhibit pursuant to Item 15(a)(3) of Form 10-K.

^ Certain exhibits and schedules to these agreements have been omitted pursuant to Item 601 of Regulation S-K. The registrant will furnish copies of any of the exhibits and schedules to the Securities and Exchange Commission upon request.

Item 16. Form 10-K Summary

None.

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**.**

CRISPR Therapeutics AG

Date: February 21, 2023

By: /s/ Samarth Kulkarni
Samarth Kulkarni
Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned directors and officers of CRISPR Therapeutics AG (the "Company"), hereby severally constitute and appoint Rodger Novak, Samarth Kulkarni, Brendan Smith and James R. Kasinger, and each of them singly, our true and lawful attorneys, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this Power of Attorney.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Samarth Kulkarni Samarth Kulkarni	Chief Executive Officer and Director (Principal Executive Officer)	February 21, 2023
/s/ Brendan Smith Brendan Smith	Chief Financial Officer (Principal Financial and Accounting Officer)	February 21, 2023
/s/ Rodger Novak Rodger Novak	President and Director	February 21, 2023
/s/ Ali Behbahani Ali Behbahani	Director	February 21, 2023
/s/ Bradley Bolzon Bradley Bolzon	Director	February 21, 2023
/s/ Maria Fardis Maria Fardis	Director	February 21, 2023
/s/ H. Edward Fleming, Jr. H. Edward Fleming, Jr.	Director	February 21, 2023
/s/ Simeon J. George Simeon J. George	Director	February 21, 2023
/s/ John Greene John Greene	Director	February 21, 2023
/s/ Katherine High Katherine High	Director	February 21, 2023
/s/ Douglas Treco Douglas Treco	Director	February 21, 2023
/s/ Brendan Smith Brendan Smith	Authorized Representative in the United States	February 21, 2023

CRISPR Therapeutics AG

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and the Board of Directors of CRISPR Therapeutics AG

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of CRISPR Therapeutics AG (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive (loss) income, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 21, 2023 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the 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 audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

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

Estimation of Variable Consideration for ongoing Collaboration Agreements

Description of the Matter

As discussed in Note 8 to the consolidated financial statements, the Company has multiple ongoing collaboration agreements which include rights to future payments totaling up to approximately $2.2 billion as of December 31, 2022 that are payable upon the achievement of various developmental, regulatory and commercial milestones related to certain programs under development. These future payments represent variable consideration that is included in the transaction price for these collaboration agreements to the extent that the Company determines it is probable that a significant revenue reversal of cumulative revenue recognized under the contract will not occur. When the Company cannot conclude that it is probable that a significant revenue reversal of cumulative revenue under the contract will not occur, the Company constrains the related variable consideration resulting in its exclusion from the transaction price. The Company's estimation of variable consideration to be constrained impacts the reported amounts of revenue and deferred revenue within the consolidated financial statements.

In determining the portion of the transaction price to be constrained, management considers the probability and uncertainty of whether the related developmental, regulatory and commercial milestones will be achieved given the nature of clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, management considers both internal and external information available including information from industry publications, the stage of development of the underlying programs and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the financial reporting period. As a result, auditing the accounting for the application of constraint to variable consideration required complex auditor judgement.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's revenue recognition process. For example, we tested controls over management's estimation of the total transaction price for its collaboration agreements including those related to the application of constraint to variable consideration associated with future developmental, regulatory and commercial milestones.

To audit the Company's judgements related to the application of constraint to variable consideration, we performed audit procedures that included, among others, evaluating the Company's judgements related to the probability of achieving the related future developmental, regulatory and commercial milestones. To evaluate the Company's estimated probability of achieving developmental, regulatory and commercial milestones, we considered the nature of clinical development and the stage of development of the underlying programs in relation to relevant external data and compared the probabilities of achieving the milestones to current industry trends and available information from other guideline companies within the same industry and other relevant factors. We also discussed the probability of achieving the milestones in relation to each program's phase of development with the Company's research and development managers.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.
Boston, Massachusetts
February 21, 2023

CRISPR Therapeutics AG
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 211,885	$ 923,031
Marketable securities	1,603,433	1,456,098
Accounts receivable	—	305
Prepaid expenses and other current assets	37,708	38,079
Total current assets	1,853,026	2,417,513
Property and equipment, net	163,634	137,575
Marketable securities, non-current	53,130	—
Intangible assets, net	71	125
Restricted cash	11,635	16,913
Operating lease assets	156,921	174,460
Other non-current assets	4,640	5,291
Total assets	$ 2,243,057	$ 2,751,877
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable	$ 27,428	$ 14,816
Accrued expenses	77,682	91,003
Deferred revenue, current	—	1,011
Accrued tax liabilities	135	724
Operating lease liabilities	15,842	12,158
Other current liabilities	20	171
Total current liabilities	121,107	119,883
Deferred revenue, non-current	12,323	12,323
Operating lease liabilities, net of current portion	228,179	212,872
Other non-current liabilities	5,969	7,339
Total liabilities	367,578	352,417
Commitments and contingencies (Note 9)		
Shareholders' equity:		
Common shares, CHF 0.03 par value, 150,347,467 and 145,364,335 shares authorized at December 31, 2022 and 2021, respectively, 78,692,766 and 77,170,382 shares issued at December 31, 2022 and 2021, respectively, 78,512,450 and 76,990,066 shares outstanding at December 31, 2022 and 2021, respectively.	2,441	2,391
Treasury shares, at cost, 180,316 shares at December 31, 2022 and 2021, respectively	(63)	(63)
Additional paid-in capital	2,734,838	2,598,114
Accumulated deficit	(846,090)	(195,915)
Accumulated other comprehensive loss	(15,647)	(5,067)
Total shareholders' equity	1,875,479	2,399,460
Total liabilities and shareholders' equity	$ 2,243,057	$ 2,751,877

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Operations and Comprehensive (Loss) Income
(In thousands, except share and per share data)

	Years Ended December 31,		
	2022	2021	2020
Revenue:			
Collaboration revenue	$ 436	$ 913,081	$ 543
Grant revenue	762	1,882	176
Total revenue	1,198	914,963	719
Operating expenses:			
Research and development	461,645	340,567	221,382
General and administrative	102,464	99,690	85,747
Collaboration expense, net	110,250	101,178	48,025
Total operating expenses	674,359	541,435	355,154
(Loss) income from operations	(673,161)	373,528	(354,435)
Other income:			
Other income, net	22,661	6,003	6,379
Total other income, net	22,661	6,003	6,379
Net (loss) income before income taxes	(650,500)	379,531	(348,056)
Benefit (provision) for income taxes	325	(1,870)	(809)
Net (loss) income	(650,175)	377,661	(348,865)
Foreign currency translation adjustment	(80)	(11)	40
Unrealized loss on marketable securities	(10,500)	(4,973)	(130)
Comprehensive (loss) income	$ (660,755)	$ 372,677	$ (348,955)
Net (loss) income per common share — basic	$ (8.36)	$ 4.97	$ (5.29)
Basic weighted-average common shares outstanding	77,746,575	75,948,686	65,949,672
Net (loss) income per common share — diluted	$ (8.36)	$ 4.70	$ (5.29)
Diluted weighted-average common shares outstanding	77,746,575	80,393,496	65,949,672

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Shareholders' Equity
(In thousands, except share and per share data)

	Common Shares		Treasury Shares		Additional			
	Shares	CHF 0.03 Par Value	Shares	Amount, at cost	Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive (Loss) Income	Total Shareholders' Equity
Balance at December 31, 2019	60,783,799	$ 1,847	250,226	$ (63)	$ 1,162,345	$ (224,711)	$ 7	$ 939,425
Issuance of common shares, net of issuance costs of $46.4 million	11,412,519	366	—	—	973,015	—	—	973,381
Vesting of restricted shares	204,650	7	—	—	—	—	—	7
Exercise of vested options, net of issuance costs of $1.2 million	1,482,636	57	(37,080)	—	32,718	—	—	32,775
Purchase of common stock under ESPP	13,410	—	—	—	694	—	—	694
Stock-based compensation expense	—	—	—	—	66,018	—	—	66,018
Issuance of common stock for license agreements	17,830	—	(17,830)	—	889	—	—	889
Other comprehensive loss	—	—	—	—	—	—	(90)	(90)
Net loss	—	—	—	—	—	(348,865)	—	(348,865)
Balance at December 31, 2020	73,914,844	$ 2,277	195,316	$ (63)	$ 2,235,679	$ (573,576)	$ (83)	$ 1,664,234
Issuance of common shares, net of issuance costs of $5.4 million	1,353,121	45	—	—	222,130	—	—	222,175
Vesting of restricted shares	455,440	15	—	—	—	—	—	15
Exercise of vested options, net of issuance costs of $2.6 million	1,245,071	54	(15,000)	—	35,820	—	—	35,874
Purchase of common stock under ESPP	21,590	—	—	—	2,095	—	—	2,095
Stock-based compensation expense	—	—	—	—	102,390	—	—	102,390
Other comprehensive loss	—	—	—	—	—	—	(4,984)	(4,984)
Net income	—	—	—	—	—	377,661	—	377,661
Balance at December 31, 2021	76,990,066	$ 2,391	180,316	$ (63)	$ 2,598,114	$ (195,915)	$ (5,067)	$ 2,399,460
Issuance of common shares	12,365	—	—	—	970	—	—	970
Vesting of restricted shares	237,932	8	—	—	—	—	—	8
Exercise of vested options, net of issuance costs of $0.9 million	1,235,528	42	—	—	35,771	—	—	35,813
Purchase of common stock under ESPP	36,559	—	—	—	2,036	—	—	2,036
Stock-based compensation expense	—	—	—	—	97,947	—	—	97,947
Other comprehensive loss	—	—	—	—	—	—	(10,580)	(10,580)
Net loss	—	—	—	—	—	(650,175)	—	(650,175)
Balance at December 31, 2022	78,512,450	$ 2,441	180,316	$ (63)	$ 2,734,838	$ (846,090)	$ (15,647)	$ 1,875,479

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Cash Flows
(In thousands)

	Years Ended December 31,		
	2022	**2021**	**2020**
Operating activities			
Net (loss) income	$ (650,175)	$ 377,661	$ (348,865)
Reconciliation of net (loss) income to net cash used in operating activities:			
Depreciation and amortization	24,172	17,953	9,184
Equity-based compensation	97,947	102,390	66,018
Other non-cash items, net	12,470	14,109	1,857
Changes in:			
Accounts receivable	305	(161)	(45)
Prepaid expenses and other assets	1,598	(13,912)	17,338
Accounts payable and accrued expenses	5,164	37,514	25,747
Deferred revenue	(1,011)	(783)	1,381
Operating lease assets and liabilities	15,310	9,506	(473)
Other liabilities, net	(1,521)	(5,305)	(10,508)
Net cash (used in) provided by operating activities	(495,741)	538,972	(238,366)
Investing activities			
Purchase of property, plant and equipment	(37,188)	(81,705)	(18,358)
Purchases of marketable securities	(1,417,800)	(1,509,327)	(593,998)
Maturities of marketable securities	1,196,333	555,602	71,186
Net cash used in investing activities	(258,655)	(1,035,430)	(541,170)
Financing activities			
Proceeds from issuance of common shares, net of issuance costs	970	213,267	982,289
Proceeds from exercise of options and ESPP contributions, net of issuance costs	37,622	37,678	33,863
Net cash provided by financing activities	38,592	250,945	1,016,152
Effect of exchange rate changes on cash	(80)	(11)	40
(Decrease) increase in cash	(715,884)	(245,524)	236,656
Cash, cash equivalents and restricted cash, beginning of period	939,944	1,185,468	948,812
Cash, cash equivalents and restricted cash, end of period	$ 224,060	$ 939,944	$ 1,185,468
Supplemental disclosure of non-cash investing and financing activities			
Property and equipment purchases in accounts payable and accrued expenses	$ 2,121	$ 8,348	$ 3,412
Equity issuance costs in accounts payable and accrued expenses	$ 99	$ 334	$ 9,590

Reconciliation to amounts within the consolidated balance sheets	As of December 31,		
	2022	**2021**	**2020**
Cash and cash equivalents	211,885	923,031	1,168,620
Prepaid expenses and other current assets	540	—	—
Restricted cash	11,635	16,913	16,848
Total	$ 224,060	$ 939,944	$ 1,185,468

See accompanying notes to these consolidated financial statements.

1. Organization and Operations

CRISPR Therapeutics AG ("CRISPR" or the "Company") was incorporated on October 31, 2013 in Basel, Switzerland. The Company was established to translate CRISPR/Cas9, a genome editing technology, into transformative gene-based medicines for the treatment of serious human diseases. The foundational intellectual property underlying the Company's operations was licensed to the Company in April 2014. The Company devotes substantially all of its efforts to product research and development activities, initial market development and raising capital. The Company's principal offices are in Zug, Switzerland, with the U.S. headquarters for research and development in Boston, Massachusetts, additional research and development based in San Francisco, CA, and a cell therapy manufacturing facility in Framingham, Massachusetts.

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations and ability to transition from pilot-scale manufacturing to large-scale production of products.

The Company had an accumulated deficit of $846.1 million as of December 31, 2022 and has financed its operations to date from a series of preferred shares and convertible loan issuances, proceeds obtained from its initial public offering, subsequent public offerings of its common shares, as well as upfront fees and milestones received under its collaboration and joint venture arrangements. The Company will require additional capital to fund its research and development and ongoing operating expenses.

As of December 31, 2022, the Company had cash, cash equivalents and marketable securities of $1,868.4 million. While the Company was in a net income position in certain previous years due to upfronts associated with the Company's collaborations with Vertex Pharmaceuticals Incorporated and certain of its subsidiaries, or Vertex, the Company has a history of recurring losses and expects to continue to incur losses for the foreseeable future. The Company expects its cash and cash equivalents will be sufficient to fund current planned operations for at least the next twenty-four months.

The full extent of the impact of the coronavirus pandemic on the Company's business, operations and financial results will depend on numerous evolving factors that we may not be able to accurately predict. See Item 1A: "Risk Factors" section set forth in this Annual Report on Form 10-K for additional details. At this stage, the impact on the Company's results has not been significant.

2. Summary of Significant Accounting Policies and Basis of Presentation

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America, or GAAP, and include the accounts of the Company and its wholly-owned subsidiaries as of December 31, 2022. All intercompany accounts and transactions have been eliminated. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification, or ASC, and Accounting Standards Updates, or ASUs, of the Financial Accounting Standards Board.

Beginning in 2022, collaboration costs under the Vertex Agreements accounted for under ASC 808, *Collaborative Agreements*, or ASC 808, are presented within "collaboration expense, net" in the consolidated statements of operations and comprehensive (loss) income. As a result, collaboration costs under the Vertex Agreements accounted for under ASC 808 for years ended December 31, 2021 and 2020 have been reclassified to conform to the current presentation. No subtotals in the prior period's consolidated financial statements were impacted. Refer to Note 8 to these consolidated financial statements for further discussion on the Vertex Agreements.

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, revenue recognition, equity-based compensation expense and reported amounts of research and development expenses during the period. Significant estimates in these consolidated financial statements have been made in connection with revenue recognition and equity-based compensation expense. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

Segment Information

The Company and the Company's chief operating decision maker, namely, the chief executive officer, view the Company's operations and manage its business as one operating segment, which is the business of discovering, developing and commercializing therapies derived from or incorporating genome-editing technology.

Foreign Currency Translation and Transactions

The majority of the Company's operations occur in entities that have the U.S. dollar as their functional currency. Non-U.S. dollar denominated functional currency subsidiaries have assets and liabilities translated into U.S. dollars at rates of exchange in effect at the end of the year. Revenue and expense amounts are translated using the average exchange rates for the period. Net unrealized gains and losses resulting from foreign currency translation are included in "Accumulated other comprehensive (loss) income." Net foreign currency exchange transaction gains or losses are included in "Other income, net" on the Company's consolidated statement of operations, the impact of which is not significant.

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of three months or less from the purchase date to be cash equivalents. As of December 31, 2022 and 2021, the Company had $211.9 million and $923.0 million in cash and cash equivalents, respectively.

Restricted Cash

As of December 31, 2022 and 2021, the Company had $12.2 million and $16.9 million, respectively, in restricted cash representing letters of credit securing the Company's obligations under certain leased facilities, as well as certain credit card arrangements. The letters of credit are secured by cash held in a restricted depository account, with $0.5 million and $0.0 million, respectively, included in prepaid expenses and other current assets in the accompanying consolidated balance sheets as of December 31, 2022 and 2021, and $11.6 million and $16.9 million, respectively, included in restricted cash in the accompanying consolidated balance sheets as of December 31, 2022 and 2021.

Marketable Securities

As of December 31, 2022 and 2021, the Company had $1,656.6 million and $1,456.1 million, respectively in marketable securities. The Company's investment strategy is focused on capital preservation. The Company invests in instruments that meet the credit quality standards outlined in the Company's investment policy. The Company classifies marketable securities with a remaining maturity, when purchased, of greater than three months as available-for-sale. Marketable securities are classified as current assets on the consolidated balance sheets if the marketable securities are available to be converted into cash to fund current operations. Marketable securities in an unrealized loss position for greater than one year with a remaining maturity date greater than one year are classified as non-current assets.

Marketable securities classified as Level 2 within the valuation hierarchy generally consist of U.S. treasury securities and government agency securities, corporate bonds, and commercial paper. Debt securities are carried at fair value with the unrealized gains and losses included in other comprehensive (loss) income as a component of stockholders' equity until realized. Any premium arising at purchase is amortized to interest expense over the period of the earliest call date, and any discount arising at purchase is accreted to interest income over the life of the instrument. Realized gains and losses on debt securities are determined using the specific identification method and are included in other income, net.

The Company assesses its available-for-sale debt securities under the available-for-sale debt security impairment model in ASU 2016-13, *Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Statements*, or ASC 326, as of each reporting date in order to determine if a portion of any decline in fair value below carrying value recognized on its available-for-sale debt securities is the result of a credit loss. The Company records credit losses in the consolidated statements of operations and comprehensive loss as credit loss expense within other expense, net, which is limited to the difference between the fair value and the amortized cost of the security. To date, the Company has not recorded any credit losses on its available-for-sale debt securities.

Other Receivables

Amounts due from collaboration partners where an arrangement is accounted for under ASC 808 are considered other receivables and are included within prepaid and other current assets in the consolidated balance sheets. Other receivables consisted of $11.2 million and $8.4 million as of December 31, 2022 and 2021, respectively and are due from Vertex. Other receivables are

recorded at invoiced amounts due under the Vertex collaboration agreement, as described further in Note 8. Vertex is a creditworthy entity that maintains an ongoing relationship with the Company and as such, the Company does not have an allowance for estimated credit losses recorded related to these other receivables.

Concentrations of Credit Risk and Off-balance Sheet Risk

Financial instruments that potentially subject the Company to concentrations of credit risk are primarily cash, cash equivalents and marketable securities. The Company's cash is held in accounts with financial institutions that management believes are creditworthy. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no financial instruments with off-balance sheet risk of loss.

Fair Value of Financial Instruments

The Company has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements:

Level 1 — Quoted prices in active markets that are accessible at the market date for identical unrestricted assets or liabilities.

Level 2 — Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs for which all significant inputs are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

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 in 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 marketable securities (see Note 3, *Marketable Securities*, and Note 4, *Fair Value Measurement*). The carrying amount of accounts receivable, other receivables, accounts payable and accrued expenses as reported on the consolidated balance sheets as of December 31, 2022 and 2021, approximate fair value, due to the short-term duration of these instruments.

Property and Equipment

Property and equipment are recorded at cost, less accumulated depreciation. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, which are as follows:

Asset	Estimated useful life
Computer equipment	3 years
Furniture, fixtures and other	5 years
Laboratory equipment	5 years
Leasehold improvements	Shorter of useful life or remaining lease term

Impairment of Long-lived Assets

The Company reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value, which is measured based on the projected discounted future net cash flows arising from the assets.

Revenue Recognition

The Company records revenue in accordance with ASC Topic 606, *Revenue from Contracts with Customers*, or ASC 606. ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases and

collaboration arrangements. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps:

1) Identify the contract with the customer

A contract with a customer exists when (i) the Company enters into an enforceable contract with a customer that defines each party's rights regarding the goods or services to be transferred and identifies the related payment terms, (ii) the contract has commercial substance and (iii) the Company determines that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

2) Identify the performance obligations in the contract

Performance obligations promised in a contract are identified based on the goods and services that will be transferred to the customer that are both capable of being distinct, whereby the customer can benefit from the good or service either on its own or together with other available resources, and are distinct in the context of the contract, whereby the transfer of the good or service is separately identifiable from other promises in the contract. To the extent a contract includes multiple promised goods and services, the Company must apply judgment to determine whether promised goods and services are capable of being distinct and distinct in the context of the contract. If these criteria are not met, the promised goods and services are accounted for as a combined performance obligation.

3) Determine the transaction price

The transaction price is determined based on the consideration to which the Company will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration such as research, development, regulatory and commercial milestones, the Company determines if it is probable that it will receive such amounts and there is no risk of a significant revenue reversal. When the Company cannot conclude that receipt of such amounts is probable, the Company constrains the related variable consideration resulting in its exclusion from transaction consideration. In determining the portion of the transaction consideration to be constrained, the Company considers the probability and uncertainty that the related research, developmental, regulatory and commercial milestones will be achieved given the nature of research and clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, the Company considers both internal and external information available, including information from industry publications and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

4) Allocate the transaction consideration to performance obligations in the contract

If the contract contains a single performance obligation, the entire transaction consideration is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction consideration to each performance obligation on a relative standalone selling price basis unless the transaction consideration is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. In determining these estimated standalone selling prices, the Company makes a number of significant judgements including, for licenses, management's assumptions regarding probability weighted projected discounted cash flows for each of the collaboration development programs. The estimated standalone selling prices are sensitive to changes in assumptions, such as probabilities of scientific success, discount rate and certain assumptions that form the basis of forecasted cash flows. In developing these assumptions, management considers both internal and external information available, including information from other guideline companies within the same industry and other relevant factors. Changes to these assumptions can have a material effect on the allocation of the transaction consideration to performance obligations, as well as the amount and timing of revenue recognized.

5) Recognize revenue when or as the Company satisfies a performance obligation

The Company satisfies performance obligations over time or at a point in time, depending on the nature of the performance obligation. Revenue is recognized over time if the customer simultaneously receives and consumes the benefits provided by the entity's performance, the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or the entity's performance does not create an asset with an alternative use to the entity and the entity has an enforceable right to payment for performance completed to date. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

Contract Balances

The Company recognizes a contract asset when the Company transfers goods or services to a customer before the customer pays consideration or before payment is due, excluding any amounts presented as an account or other receivable. A contract asset is an entity's right to consideration in exchange for goods or services that the entity has transferred to a customer. The contract liabilities, or deferred revenue, primarily relate to contracts where we have received payment, but we have not yet satisfied the related performance obligations. Contract assets are not significant as of December 31, 2022 and 2021. Contract liabilities recorded as deferred revenue as of December 31, 2022 are $12.3 million, which was unchanged from December 31, 2021. The contract liability recorded as deferred revenue is related to the collaboration agreement with Vertex described in Note 8.

Collaboration Arrangements

The Company records the elements of its collaboration agreements that represent joint operating activities in accordance with ASC 808. Accordingly, the elements of the collaboration agreements that represent activities in which both parties are active participants and to which both parties are exposed to the significant risks and rewards that are dependent on the commercial success of the activities, are recorded as collaborative arrangements.

The Company evaluates the proper presentation of the commercial activities and the profit and loss sharing associated with the collaboration agreements. ASC 808 states that when payments between parties in a collaborative arrangement are not within the scope of other authoritative accounting literature, the income statement classification should be based on the nature of the arrangement, the nature of its business operations and the contractual terms of the arrangement. To the extent that these payments are not within the scope of other authoritative accounting literature, the income statement classification for the payments shall be based on an analogy to authoritative accounting literature or if there is no appropriate analogy, a reasonable, rational and consistently applied accounting policy election.

Collaboration costs under the Vertex Agreements accounted for under ASC 808 are presented within "collaboration expense, net" in the consolidated statements of operations and comprehensive (loss) income. Refer to Note 8 to these consolidated financial statements for further discussion on the Vertex Agreements.

Research and Development Expenses

Research and development costs are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, license and milestone fees, contract services and other related costs. Research and development costs, including up-front fees and milestones paid to collaborators, are also expensed as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense. The Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants or other clinical trial vendors that perform the activities. The Company recognizes the reimbursement associated with collaborative activities to its collaborative partners, excluding collaboration costs under the Vertex Agreements accounted for under ASC 808, as a reduction to research and development expense in the period the services are provided. Costs associated with collaborative activities to collaborative partners accounted for under ASC 808 and included in research and development expense was not significant for the years ended December 31, 2022, 2021 and 2020

Leases

The Company accounts for its leases in accordance with ASC 842, *Leases*, or ASC 842. At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company does not have financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty of renewal.

Assumptions made by the Company at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

Equity Based Compensation Expense

The Company's share-based compensation programs grant awards that have included stock options, restricted stock units and restricted stock awards. Grants are awarded to employees and non-employees, including directors.

The Company accounts for its stock-based compensation awards in accordance with ASC Topic 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees and non-employee directors, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive (loss) income based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

The Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

The Company's stock-based awards are subject to service or performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company expenses restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award.

The Company estimates the fair value of its option awards to employees, directors and non-employees using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of complete company-specific historical and implied volatility data for the full expected term of the stock-based awards, the Company bases its estimate of expected volatility on a representative group of publicly traded companies in addition to its own volatility data. For these analyses, the Company selected companies with comparable characteristics to its own, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The Company computes historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The Company has estimated the expected term of its employee stock options using the "simplified" method, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option, due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future.

Patent Costs

Costs to secure and prosecute patent applications and other legal costs related to the protection of the Company's intellectual property are expensed as incurred and are classified as general and administrative expenses in the Company's consolidated statements of operations.

Income Taxes

Income taxes are recorded in accordance with ASC Topic 740, *Income Taxes*, or ASC 740, which provides for deferred taxes using an asset and liability approach. Under this method, deferred tax assets and liabilities are determined based on the difference

between the financial reporting and tax reporting basis of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when 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 of the deferred tax assets will not be realized. The Company has evaluated available evidence and concluded that the Company may not realize all the benefit of its deferred tax assets; therefore, a valuation allowance has been established for the amount of the deferred tax assets that the Company does not believe is more likely than not to be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. 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 does not have any significant uncertain tax positions. The Company's practice is to recognize interest and/or penalties related to income tax matters in income tax expense. See Note 14 for further details.

Comprehensive (Loss) Income

Comprehensive (loss) income consists of net income or loss and other comprehensive (loss) income. Other comprehensive (loss) income consists of foreign currency translation adjustments and unrealized losses on marketable securities.

Net (Loss) Income Per Share Attributable to Common Shareholders

Basic net (loss) income per share is calculated by dividing net (loss) income attributable to common shareholders by the weighted-average number of common shares outstanding during the period. Diluted net (loss) income per share is calculated by dividing the net (loss) income attributable to common shareholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options and restricted stock units using the treasury stock method. See Note 12 for further details.

New Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies that the Company adopts as of the specified effective date. The Company does not believe that the adoption of recently issued standards have or may have a material impact on its consolidated financial statements and disclosures.

3. Marketable Securities

A summary of the Company's cash equivalents and marketable securities as of December 31, 2022 and 2021, which are recorded at fair value (and excludes $159.3 million and $405.6 million of cash at December 31, 2022 and 2021, respectively) is shown below (in thousands):

December 31, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Cash equivalents:				
Money market funds	$ 17,766	$ —	$ —	$ 17,766
Corporate debt securities	2,151	—	(2)	2,149
Certificates of deposit	—	—	—	—
Commercial paper	32,675	—	—	32,675
Total cash equivalents	52,592	—	(2)	52,590
Marketable securities:				
U.S. Treasury securities	—	—	—	—
Corporate debt securities	1,236,770	615	(15,006)	1,222,379
Certificates of deposit	92,417	—	—	92,417
Government-sponsored enterprise securities	79,746	11	(712)	79,045
Commercial paper	263,231	—	(509)	262,722
Total marketable securities	1,672,164	626	(16,227)	1,656,563
Total cash equivalents and marketable securities	$ 1,724,756	$ 626	$ (16,229)	$ 1,709,153

December 31, 2021	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Cash equivalents:				
Money market funds	$ 507,386	$ —	$ —	$ 507,386
Corporate debt securities	—			—
Certificates of deposit	—	—	—	—
Commercial paper	9,997	—	(1)	9,996
Total cash equivalents	517,383	—	(1)	517,382
Marketable securities:				
U.S. Treasury securities	16,238	6	(52)	16,192
Corporate debt securities	1,173,659	10	(4,903)	1,168,766
Certificates of deposit	45,164	—	—	45,164
Government-sponsored enterprise securities	13,334	—	(77)	13,257
Commercial paper	212,805	—	(86)	212,719
Total marketable securities	1,461,200	16	(5,118)	1,456,098
Total cash equivalents and marketable securities	$ 1,978,583	$ 16	$ (5,119)	$ 1,973,480

As of December 31, 2022 and 2021, the aggregate fair value of marketable securities that were in an unrealized loss position for less than twelve months was $628.4 million and $1,311.6 million, respectively. As of December 31, 2022 and 2021, the aggregate fair value of marketable securities that were in an unrealized loss position for more than twelve months was $619.2 million and $4.6 million, respectively. Of this amount, securities totaling $53.1 million as of December 31, 2022 will mature beyond one year. No securities in an unrealized loss position for more than twelve months as of December 31, 2021 will mature beyond one year. The Company has recorded a net unrealized loss of $10.5 million and $5.0 million, respectively, during the years ended December 31, 2022 and 2021 related to its marketable securities, which is included in comprehensive (loss) income on the consolidated statements of operations and comprehensive (loss) income.

The Company determined that there was no material credit risk of the above investments as of December 31, 2022 and 2021. The Company has the intent and ability to hold such securities until recovery. As a result, the Company did not record any charges for credit-related impairments for its marketable securities for the years ended December 31, 2022 and 2021. No available-for-sale debt securities held as of December 31, 2022 had remaining maturities greater than thirty months.

4. Fair Value Measurement

The following tables present information about the Company's financial assets measured at fair value on a recurring basis and indicate the fair value hierarchy classification of such fair values as of December 31, 2022 and 2021 (in thousands):

	Fair Value Measurements at December 31, 2022			
	Total	Level 1	Level 2	Level 3
Cash and cash equivalents:				
Cash	$ 159,295	$ 159,295	$ —	$ —
Money market funds	17,766	17,766	—	—
Corporate debt securities	2,149	—	2,149	—
Certificates of deposit	—	—	—	—
Commercial paper	32,675	—	32,675	—
Marketable securities:				
U.S. Treasury securities	—	—	—	—
Corporate debt securities	1,222,379	—	1,222,379	—
Certificates of deposit	92,417	—	92,417	—
Government-sponsored enterprise securities	79,045	—	79,045	—
Commercial paper	262,722	—	262,722	—
Other non-current assets	2,212	—	—	2,212
Total	$ 1,870,660	$ 177,061	$ 1,691,387	$ 2,212

	Fair Value Measurements at December 31, 2021			
	Total	Level 1	Level 2	Level 3
Cash and cash equivalents:				
Cash	$ 405,648	$ 405,648	$ —	$ —
Money market funds	507,386	507,386	—	—
Corporate debt securities	—	—	—	—
Certificates of deposit	—	—	—	—
Commercial paper	9,997	—	9,997	—
Marketable securities:				
U.S. Treasury securities	16,192	—	16,192	—
Corporate debt securities	1,168,766	—	1,168,766	—
Certificates of deposit	45,164	—	45,164	—
Government-sponsored enterprise securities	13,257	—	13,257	—
Commercial paper	212,719	—	212,719	—
Other non-current assets	2,212	—	—	2,212
Total	$ 2,381,341	$ 913,034	$ 1,466,095	$ 2,212

Marketable securities classified as Level 2 within the valuation hierarchy generally consist of U.S. treasury securities and government agency securities, corporate bonds, and commercial paper. The Company estimates the fair values of these marketable securities by taking into consideration valuations obtained from third-party pricing sources.

The Company holds equity securities classified as Level 3 which are not material to the Company's financial position.

5. Property and Equipment, net

Property and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2022	2021
Computer equipment	$ 3,618	$ 1,757
Furniture, fixtures, and other	8,109	4,371
Laboratory equipment	37,897	30,123
Leasehold improvements	141,680	86,735
Construction work in process	6,162	52,396
Total property and equipment, gross	197,466	175,382
Accumulated Depreciation	(33,832)	(37,807)
Total property and equipment, net	$ 163,634	$ 137,575

Depreciation expense for the year ended December 31, 2022, 2021 and 2020 was $24.1 million, $17.9 million, and $9.1 million, respectively.

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2022	2021
Payroll and employee-related costs	$ 19,241	$ 23,661
Research costs	46,187	47,986
Licensing fees	983	138
Professional fees	4,927	4,720
Intellectual property costs	3,936	6,120
Accrued property and equipment	1,244	7,113
Other	1,164	1,265
Total	$ 77,682	$ 91,003

7. Leases

In June 2015, the Company entered into a lease agreement for the lease of research facility space in Cambridge, Massachusetts, with a commencement date of November 15, 2015. The lease was subsequently amended in both 2017 and 2020 and expired in 2022.

In May 2016, the Company entered into a sublease agreement for its primary office and research facility in Cambridge, Massachusetts, with a commencement date of December 23, 2016. The sublease was subsequently amended in 2021 and expired in 2022.

In May 2019, the Company entered into a lease agreement for office facility space in Cambridge, Massachusetts, with a commencement date of June 1, 2019, or the 2019 Lease. The lease expires in November 2026, and the Company has an option to extend the term of the lease for an additional five-year period based on certain conditions within the Company's control. The 2019 Lease contains escalating rent clauses which require higher rent payments in future years. The right-of-use asset and corresponding lease liability does not include the additional five-year period under the renewal option as the Company is not reasonably certain to exercise that option.

In December 2019, Casebia Therapeutics, Limited Liability Partnership, or Casebia, became a wholly-owned subsidiary of the Company. In connection therewith, Casebia assigned its sublease for an office and research facility in Cambridge, Massachusetts to the Company. The sublease was subsequently amended in 2021 and expired in 2022.

In May 2020, the Company entered into a lease agreement for a cell therapy manufacturing facility in Framingham, Massachusetts, or the Framingham Lease, for clinical and commercial production of the Company's investigational cell therapy product candidates. The Framingham Lease expires in March 2036 and the Company has an option to extend the term of the lease for two additional seven-year periods. The right-of-use asset and corresponding lease liability does not include the additional seven-year periods under the renewal option as the Company is not reasonably certain to exercise that option.

In July 2020, the Company entered into a lease agreement for an office and laboratory facility in Boston, Massachusetts, with a commencement date of June 1, 2021, or the 2020 Lease. At lease commencement, the Company recorded a right-of-use asset of $149.8 million and a corresponding operating lease liability of $147.9 million. Tenant incentives of $49.2 million were recorded as a reduction to the operating lease asset and liability at lease commencement. The lease expires in March 2034 and the Company has an option to extend the term of the lease for two additional five-year periods. The right-of-use asset and corresponding lease liability does not include the additional five-year periods under the renewal option as the Company is not reasonably certain to exercise that option.

The Company also rents certain office space in Zug, Switzerland, on a short-term basis for which a right-of-use asset and liability are not recorded, in accordance with the practical expedient elected.

The Company has embedded leases in certain research and license agreements for which the Company has recorded a right of use asset and liability. These arrangements are not significant in comparison to the Company's total operating lease assets and liabilities. In addition, the Company has identified certain short-term leases embedded within its manufacturing contracts which are not recorded on the Company's balance sheet in accordance with the practical expedient elected.

The Company identified and assessed the following estimates in recognizing the right-of-use asset and corresponding liability:

- *Expected lease term*: The expected lease term includes noncancelable lease periods and, when applicable, periods covered by an option to extend the lease if the Company is reasonably certain to exercise that option, as well as periods covered by an option to terminate the lease if the Company is reasonably certain not to exercise that option.
- *Incremental borrowing rate*: As the discount rates in the Company's leases are not implicit, the Company estimated the incremental borrowing rate based on the rate of interest the Company would have to pay to borrow a similar amount on a collateralized basis over a similar term.

The following table summarizes the lease assets and liabilities as of December 31, 2022 and 2021 (in thousands):

	As of December 31,	
	2022	2021
Assets		
Operating lease assets	$ 156,921	$ 174,460
Total lease assets	156,921	174,460
Liabilities		
Current		
Operating lease liabilities	15,842	12,158
Non-current		
Operating lease liabilities, net of current portion	228,179	212,872
Total lease liabilities	$ 244,021	$ 225,030

The following table summarizes operating lease costs included in research and development and general and administrative expense, as well as sublease income for the twelve months ended December 31, 2022, 2021 and 2020 (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Operating lease costs	$ 34,896	$ 22,520	$ 14,342
Short-term lease costs	824	11,087	7,339
Variable lease costs	11,882	8,402	6,368
Sublease income	—	(5,253)	(587)
Net lease cost	$ 47,602	$ 36,756	$ 27,462

The following table summarizes the maturity of undiscounted payments due under lease liabilities and the present value of those liabilities as of December 31, 2022 (in thousands):

	Total
2023	29,270
2024	26,526
2025	26,251
2026	26,745
2027	25,927
Thereafter	205,495
Total	$ 340,214
Present value adjustment	(96,193)
Present value of lease liabilities	$ 244,021

The following table summarizes the lease term (in years) and discount rate for operating leases as of December 31, 2022 and 2021:

	As of December 31,	
	2022	2021
Weighted-average remaining lease term	11.8	12.4
Weighted-average discount rate	5.9%	5.9%

The following table summarizes the cash paid for amounts included in the measurement of lease liabilities for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Cash paid for amounts included in measurement of lease liabilities:			
Operating cash flows used in operating leases	$ (17,004)	$ (19,753)	$ (13,161)
Operating lease non-cash items:			
Right-of-use assets (decreased) increased through lease modifications and reassessments	1,208	(14,230)	3,169
Right-of-use assets obtained in exchange for operating lease liabilities	—	152,486	13,956
Leasehold improvements paid directly by landlord	19,252	30,500	—

8. Significant Contracts

Agreements with Vertex Pharmaceuticals Incorporated and certain of its subsidiaries

Summary

On October 26, 2015, the Company entered into a strategic collaboration, option and license agreement, or the 2015 Collaboration Agreement, with Vertex. The 2015 Collaboration Agreement is focused on the use of the Company's CRISPR/Cas9 gene editing technology to discover and develop potential new treatments aimed at the underlying genetic causes of human disease.

On December 12, 2017, the Company and Vertex entered into Amendment No. 1 to the 2015 Collaboration Agreement, or Amendment No. 1, and the Joint Development Agreement, or the JDA. Amendment No. 1, among other things, modified certain definitions and provisions of the 2015 Collaboration Agreement to make them consistent with the JDA and clarified how many options are exercised (or deemed exercised) in connection with certain targets specified under the 2015 Collaboration Agreement. Amendment No. 1 also amended other provisions of the 2015 Collaboration Agreement, including the expiration terms.

In connection with the 2015 Collaboration Agreement, Vertex made a nonrefundable upfront payment of $75.0 million. Under the 2015 Collaboration Agreement, Vertex agreed to fund the discovery activities conducted pursuant to the agreement while retaining options to co-exclusive and exclusive licenses. In December 2017, upon execution of the JDA and Amendment No. 1, Vertex exercised its option to obtain a co-exclusive license to develop and commercialize hemoglobinopathy and beta-globin targets. As such, for potential hemoglobinopathy treatments, including treatments for sickle cell disease, the Company and Vertex agreed to share equally all research and development costs and worldwide revenues. In connection with the JDA, the Company received a $7.0 million up-front payment from Vertex and subsequently received a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate. In addition, upon execution of the JDA and Amendment No. 1, it was clarified that Vertex may elect to license up to four remaining targets, for which it will lead global development and commercialization activities, and the Company received the right to receive up to $420.0 million in development, regulatory and commercial milestones and royalties on net product sales for each of the targets (inclusive of $10 million due upon exercise of each exclusive option).

In June 2019, the Company and Vertex entered into a series of agreements, which closed in the second quarter of 2019, including a strategic collaboration and license agreement, or the 2019 Collaboration Agreement, for the development and commercialization of products for the treatment of Duchenne muscular dystrophy, or DMD, and Myotonic Dystrophy Type 1, or DM1. Under the terms of the 2019 Collaboration Agreement, the Company received an upfront, nonrefundable payment of $175.0 million. In addition, the Company was initially eligible to receive potential aggregate payments of up to $825.0 million based upon the successful achievement of specified research, development, regulatory and commercial milestones for the DMD and DM1 programs.

The Company is also eligible to receive tiered royalties on future net sales on any products that may result from the 2019 Collaboration Agreement. For the DMD program, Vertex is responsible for all research, development, manufacturing and commercialization activities and all related costs. For the DM1 program, the Company performed specified guide RNA research and Vertex is responsible for all other research, development, manufacturing and commercialization costs. Upon Investigational New Drug, or IND, application filing, the Company has the option to forego the DM1 milestones and royalties, and instead, co-develop and co-commercialize all DM1 products globally in exchange for payment of 50% of research and development costs incurred by Vertex from the effective date of the agreement through IND filing.

In connection with the execution of the 2019 Collaboration Agreement, the Company and Vertex entered into a second amendment to the 2015 Collaboration Agreement, or Amendment No. 2. Among other things, Amendment No. 2 modified certain definitions and provisions of the 2015 Collaboration Agreement to make them consistent with the 2019 Collaboration Agreement and set forth the number and identity of the collaboration targets under the 2015 Collaboration Agreement. The Company and Vertex agreed that one of the four remaining options under the 2015 Collaboration Agreement, as amended, would not be exercised; instead, the Company reacquired the exclusive rights and agreed to conduct research and development activities for the specified target. Vertex will have the option to co-develop and co-commercialize the specified target upon IND filing in exchange for payment of 50% of research and development costs incurred by the Company from the effective date of the agreement through IND filing. If Vertex does not exercise its option to co-develop and co-commercialize the specified target, Vertex is eligible to receive up to $395.0 million in potential specified research, development, regulatory and commercial milestones and tiered single-digit royalties on future net sales.

In October 2019, Vertex exercised the remaining three options granted to it under the 2015 Collaboration Agreement to exclusively license the collaboration targets developed under the 2015 Collaboration Agreement, resulting in a payment of $30.0 million to the Company in the fourth quarter of 2019. In addition, the Company achieved the first milestone under the 2019 Collaboration Agreement in the first quarter of 2020 and, in connection therewith, received a payment of $25.0 million in April 2020. The Company achieved the second milestone under the 2019 Collaboration Agreement in the fourth quarter of 2021 and, in connection therewith, received a payment of $12.5 million in December 2021. As of December 31, 2022, the Company is eligible to receive remaining potential future milestones of $775.0 million under the 2019 Collaboration Agreement.

In April 2021, the Company and Vertex agreed to amend and restate the JDA and entered into an Amended and Restated Joint Development and Commercialization Agreement, or the "A&R Vertex JDCA," pursuant to which the parties agreed to, among other things, (a) adjust the governance structure for the collaboration and adjust the responsibilities of each party thereunder, whereby Vertex shall lead and have all decision making (i.e., control) in relation to the exa-cel program prospectively; (b) adjust the allocation of net profits and net losses between the parties with respect to exa-cel (formerly known as CTX001) only, which will be allocated 40% to the Company and 60% to Vertex, prospectively; and (c) exclusively license (subject to the Company's reserved rights to conduct certain activities) certain intellectual property rights to Vertex relating to the specified product candidates and products (including exa-cel) that may be researched, developed, manufactured and commercialized on a worldwide basis under such agreement. The transaction contemplated by the A&R Vertex JDCA closed in the second quarter of 2021. The Company is providing certain specified transition services to Vertex in connection with the agreement.

In connection with the closing of the transaction contemplated by the A&R Vertex JDCA, the Company received a $900.0 million up-front payment from Vertex. Additionally, the Company is eligible to receive a one-time $200.0 million milestone payment upon receipt by Vertex of the first marketing approval of the initial product candidate from the U.S. Food and Drug Administration or the European Commission. With respect to exa-cel only, the net profits and net losses, as applicable, incurred under the A&R Vertex JDCA through July 1, 2021 in connection with the initial shared product (i.e., exa-cel) were shared equally between the Company and Vertex, and beginning July 1, 2021, the net profits and net losses, as applicable, incurred under the A&R Vertex JDCA are allocated 40% to the Company and 60% to Vertex. Additionally, the A&R Vertex JDCA allows the Company to defer a portion of its share of costs under the arrangement if spending on the exa-cel program exceeds specified amounts. Any deferred amounts are only payable to Vertex as an offset against future profitability of the exa-cel program and the amounts payable are capped at a specified maximum amount per year.

Accounting for the Vertex Agreements

The 2015 Collaboration Agreement, Amendment No. 1, and JDA are collectively the "2015 Agreements" and the 2019 Collaboration Agreement and Amendment No. 2. are collectively the "2019 Agreements." The 2015 Collaboration Agreement, Amendment No. 1, Amendment No. 2, JDA, A&R Vertex JDCA and 2019 Collaboration Agreement are collectively the "Vertex Agreements."

The Vertex Agreements include components of a customer-vendor relationship as defined under ASC 606, collaborative arrangements as defined under ASC 808 and research and development costs as defined under ASC 730, *Research and Development*, or ASC 730.

Accounting Analysis Under ASC 606

Accounting for the A&R Vertex JDCA

Identification of the Contract

The A&R Vertex JDCA represented a contractual modification to the JDA. For accounting purposes, the A&R Vertex JDCA was treated as a separate contract.

Identification of Performance Obligations

The Company concluded the A&R Vertex JDCA contained a single material promise, an exclusive worldwide license granting Vertex an additional 10% economic interest in the exa-cel program and the right to control development and commercialization of exa-cel, or the "Exa-cel Exclusive License." The Company concluded the Exa-cel Exclusive License was both capable of being distinct and distinct within the context of the A&R Vertex JDCA, and the Exa-cel Exclusive License was sold at its estimated standalone selling price, or "ESSP." As such, the Exa-cel Exclusive License represented a separate performance obligation.

Determination of Transaction Price

The transaction price was comprised of the upfront payment of $900.0 million. The Company determined that all other possible variable consideration resulting from milestones and royalties discussed above was fully constrained at the time of the transaction. The Company will reevaluate the transaction price in each reporting period.

Allocation of Transaction Price to Performance Obligations

The selling price of the performance obligation was determined based on the Company's ESSP. The Company developed the ESSP for the Exa-cel Exclusive License with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis.

The ESSP for the Exa-cel Exclusive License was determined to be approximately $900.0 million. The ESSP was determined based on 10% of the probability and present value adjusted cash flows from projected worldwide net profit for exa-cel based on probability assessments, projections based on internal forecasts, industry data, and information from other guideline companies within the same industry and other relevant factors. As the Company determined the Exa-cel Exclusive License was the only performance obligation, the entire transaction price was allocated to the Exa-cel Exclusive License. The aforementioned ESSP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

Recognition of Revenue

The Company determined that the Exa-cel Exclusive License represented functional intellectual property, as the intellectual property provides Vertex with the ability to perform a function or task in the form of research and development, manufacturing and commercialization. As such, the revenue related to the Exa-cel Exclusive License was recognized at the point in time, which was upon transfer in the second quarter of 2021.

Accounting for the 2019 Agreements

The 2019 Agreements represented a contract modification to the 2015 Agreements. As a result, the 2019 Agreements and the 2015 Agreements are combined for accounting purposes and treated as a single arrangement. Transactions under the 2019 Agreements were not material for the twelve months ended December 31, 2022 and 2020. For the twelve months ended December 31, 2021, the Company recognized $12.0 million in revenue related to a milestone under the 2019 Agreements.

The Company determined that all other possible variable consideration remaining under the 2019 Agreements resulting from milestones and royalties discussed above was fully constrained as of December 31, 2022. The Company will re-evaluate the transaction price in each reporting period.

Revenue recognized in connection with the Vertex Agreements

Revenue recognized under the Vertex Agreements for the year ended December 31, 2022 was not material. Revenue recognized under the Vertex Agreements for the year ended December 31, 2021 was $913.1 million and was comprised of (i) revenue related to the exclusive worldwide license for exa-cel of $900.0 million, (ii) revenue related to the second DM1 milestone under the 2019 Agreements of $12.0 million, and (iii) revenue recognized in connection with research and development services. Revenue recognized under the Vertex Agreements for the year ended December 31, 2020 was not material.

As of December 31, 2022 and 2021 there was no current deferred revenue related to the collaboration with Vertex, respectively. As of December 31, 2022 and 2021, there was $12.3 million of non-current deferred revenue, respectively, related to the collaboration with Vertex. The transaction price allocated to the remaining performance obligations was $12.3 million.

Future Milestones under the Vertex Agreements

The Company has evaluated the milestones that may be received in connection with the Vertex Agreements. As discussed above, the Company is eligible to receive up to $410.0 million in additional development, regulatory and commercial milestones and royalties on net product sales for each of the three collaboration targets that Vertex licensed in the fourth quarter of 2019. Each

milestone is payable only once per collaboration target, regardless of the number of products directed to such collaboration target that achieve the relevant milestone event.

The Company is eligible to receive additional potential future payments of up to $775.0 million based upon the successful achievement of specified development, regulatory and commercial milestones for the DMD and DM1 programs. The Company is also eligible to receive tiered royalties on future net sales on any products that may result from this collaboration; however, the Company has the option to forego the DM1 milestones and royalties to co-develop and co-commercialize all DM1 products globally.

The Company is eligible to receive additional potential future payments of up to $200.0 million upon receipt by Vertex of the first marketing approval of the initial product candidate from the U.S. Food and Drug Administration or the European Commission. In addition, the Company has the option to conduct research at their own cost in certain defined areas that, if beneficial to the exa-cel program and exa-cel ultimately achieves regulatory approval in such areas, then the Company could be entitled to certain milestone payments aggregating to high eight digits from Vertex.

Each of the remaining milestones are fully constrained as of December 31, 2022. There is uncertainty that the events to obtain the research and developmental milestones will be achieved given the nature of clinical development and the stage of the CRISPR/Cas9 technology. The remaining research, development and regulatory milestones will be constrained until it is probable that a significant revenue reversal will not occur. Commercial milestones and royalties relate predominantly to a license of intellectual property and are determined by sales or usage-based thresholds. The commercial milestones and royalties are accounted for under the royalty recognition constraint and will be accounted for as constrained variable consideration. The Company applies the royalty recognition constraint for each commercial milestone and will not recognize revenue for each until the subsequent sale of a licensed product (achievement of each) occurs.

Accounting Analysis under ASC 808

In connection with the Vertex Agreements, the Company identified the following collaborative elements, which are accounted for under ASC 808: (i) development and commercialization services for shared products, including any transition services related to exa-cel under the A&R Vertex JDCA; (ii) R&D Services for follow-on products; and (iii) committee participation. The related impact of the cost sharing is included within collaboration expense, net, in the consolidated statements of operations and comprehensive (loss) income.

During the years ended December 31, 2022, 2021 and 2020, the Company recognized $110.3 million, $101.2 million, and $48.0 million of collaboration expense, net, related to the Vertex Agreements, respectively. Research and development expense for the years ended December 31, 2022, 2021 and 2020 is net of $37.8 million, $47.4 million, and $27.6 million of reimbursements from Vertex, respectively.

Under the A&R Vertex JDCA, the Company has an option to defer its portion of specified costs on the exa-cel program in excess of $110.3 million for the years ended December 31, 2022, 2023 and 2024. Vertex may only recover any such deferred amounts as an offset against future profitability of the exa-cel program, determined on an annual basis in accordance with the A&R Vertex JDCA. Any such deferred amounts are capped at a specified maximum amount per year. For the year ended December 31, 2022, the Company exercised its option to defer $36.1 million of its share of costs incurred under the A&R Vertex JDCA. These deferred costs will be recognized by the Company when recoverability of such deferred amounts by Vertex is probable and the amount can be reasonably estimated. As of December 31, 2022, no such deferred amounts have been recognized.

9. Commitments and Contingencies

Intellectual Property Agreements

Charpentier License Agreements

In April 2014, the Company entered into certain technology license agreements with Dr. Emmanuelle Charpentier pursuant to which the Company licensed certain intellectual property rights under joint ownership from Dr. Charpentier to develop and commercialize products for the treatment or prevention of human diseases. In connection therewith, Dr. Charpentier is entitled to receive nominal clinical milestone payments, low single digit percentage of sublicensing payments received under any sublicense agreement with a third party, and low single-digit percentage royalties based on annual net sales of licensed products and services by the Company and its affiliates and sublicensees.

Patent Assignment Agreement

In November 2014, the Company entered into a patent assignment agreement with Dr. Charpentier, Dr. Ines Fonfara, and Vienna (collectively, the "Assignors"), pursuant to which the Company was assigned all rights, title and interest in and to certain patent rights claimed in the U.S. Patent Application No.61/905,835. As a result, the Assignors are entitled to receive certain low single digit clinical milestone payments and low single digit royalties based on annual net sales of licensed products and licensed services by the Company, its affiliates and sublicensees.

During the years ended December 31, 2022, 2021 and 2020, the Company paid an immaterial amount of fees to Dr. Charpentier under the Charpentier License Agreements and the Assignors under the Patent Assignment Agreement, which were recorded as research and development expense.

Research, Manufacturing and License Agreements

The Company has engaged several research institutions and companies to identify new delivery strategies and applications of the Company's gene editing technology. The Company is also a party to a number of license agreements which require significant upfront payments and may be required to make future royalty payments and potential milestone payments from time to time. In addition, the Company is also a party to intellectual property agreements, which require maintenance and milestone payments from time to time. Further, the Company is a party to a number of manufacturing agreements that require upfront payments for the future performance of services.

In association with these agreements, on a product-by-product basis, the counterparties are eligible to receive up to low eight-digit potential payments upon specified research, development and regulatory milestones. In addition, on a product-by-product basis, the counterparties are eligible to receive potential commercial milestone payments based on specified annual sales thresholds. The potential payments are low-single digit percentages of the specified annual sales thresholds. The counterparties are also eligible to receive low single-digit royalties on future net sales.

Under certain circumstances and if certain contingent future events occur, Vertex is eligible to receive up to $395.0 million in potential specified research, development, regulatory and commercial milestones and tiered single-digit percentage royalties on future net sales related to a specified target under an amendment to the 2015 Collaboration Agreement. Vertex also has the option to conduct research at their own cost in certain defined areas that, if beneficial to the exa-cel program and ultimately achieves regulatory approval, then the Company could owe Vertex certain milestone payments aggregating to high eight digits, subject to certain limitations on the profitability of the exa-cel program.

Under the A&R Vertex JDCA, the Company deferred $36.1 million of its share of costs incurred under the arrangement for the year ended December 31, 2022, as spending on the exa-cel program exceeded a specified amount. Any deferred amounts are only payable to Vertex as an offset against future profitability of the exa-cel program and the amounts payable are capped at a specified maximum amount per year. These deferred costs on the exa-cel program will be accrued for when it is probable that a liability has been incurred and the amount can be reasonably estimated. As of December 31, 2022, no contingent payments have been accrued. Refer to Note 8 for further discussion on the Company's arrangements with Vertex.

Other Matters

On December 15, 2016, the Company entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement (the "Invention Management Agreement") with UC, Vienna, Dr. Charpentier, Intellia Therapeutics, Inc., Caribou Biosciences, Inc., ERS Genomics Ltd. and one of the Company's subsidiaries. Under the Invention Management Agreement, the Company is obligated to share costs related to patent maintenance, defense and prosecution. For the years ended December 31, 2022, 2021 and 2020, the Company incurred $2.2 million, $5.8 million, and $4.5 million, respectively, in shared costs. The Company recorded accrued legal costs from the cost sharing of $1.4 million and 4.0 million as of December 31, 2022 and 2021, respectively. The Company is unable to predict the outcome of these matters and is unable to make a meaningful estimate of the amount or range of loss, if any, that could result from an unfavorable outcome.

Litigation

In the ordinary course of business, the Company is from time to time involved in lawsuits, investigations, proceedings and threats of litigation related to, among other things, the Company's intellectual property estate (including certain in-licensed intellectual property), commercial arrangements and other matters. Such proceedings may include quasi-litigation, *inter partes* administrative proceedings in the U.S. Patent and Trademark Office and the European Patent Office involving the Company's intellectual property estate including certain in-licensed intellectual property. The outcome of any of the foregoing, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of Company's management and other resources that would otherwise be engaged in other activities. If the Company is unable to prevail in any such proceedings, the Company's business, results of operations, liquidity and financial condition could be adversely affected.

10. Share Capital

The Company had 150,347,467 and 145,364,335 authorized common shares as of December 31, 2022 and 2021, respectively, with a par value of CHF 0.03 per share. Share Capital consisted of the following:

		As of December 31,	
Type of Share Capital	**Conditional Capital**	**2022**	**2021**
Common shares	Registered share capital	82,028,328	80,321,227
Common shares	Authorized share capital	39,316,975	39,316,975
Common shares	Conditional share capital - Bonds or similar debt instruments	8,202,832	4,919,700
Common shares	Conditional share capital - Employee benefit plans	20,799,332	20,806,433
	Total	150,347,467	145,364,335

Included in registered share capital are 5,025,897 shares registered, of which 4,845,581 shares are held by the Company and its subsidiaries and are reserved for future issuance for financings and 180,316 shares held by the Company and its subsidiaries as treasury shares.

Common Share Issuances

Recent Public Offerings

In July 2020, the Company sold 7.4 million common shares through an underwritten public offering (inclusive of shares sold pursuant to the exercise of the underwriters' option to purchase additional shares) at a public offering price of $70.00 per share for aggregate net proceeds of $484.8 million, which were net of equity issuance costs and stamp tax of $32.5 million.

At-the-Market Offerings

In August 2019, the Company entered into an Open Market Sale Agreement℠ with Jefferies LLC, or Jefferies, under which the Company was able to offer and sell, from time to time at its sole discretion through Jefferies, as its sales agent, its common shares, or the August 2019 Sales Agreement. In August 2019, the Company filed a prospectus supplement with the SEC to offer and sell, from time to time, common shares having aggregate gross proceeds of up to $200.0 million, or the 2019 ATM. During the year ended December 31, 2020, the Company issued and sold an aggregate of 2.2 million common shares under the 2019 ATM at an average price of $89.47 per share for aggregate proceeds of $195.5 million, which were net of equity issuance costs of $4.5 million.

In December 2020, in connection with the August 2019 Sales Agreement, the Company filed a prospectus supplement with the SEC to offer and sell, from time to time, common shares having aggregate gross proceeds of up to $350.0 million, or the 2020 ATM. During the year ended December 31, 2020, the Company issued and sold an aggregate of 1.8 million common shares under the 2020 ATM at an average price of $169.57 per share for aggregate proceeds of $298.0 million, which were net of equity issuance costs of $4.5 million. Additional equity issuance costs for stamp taxes related to shares sold in 2020 related to the 2019 ATM and 2020 ATM were $4.9 million, of which $4.0 million was accrued as of December 31, 2020 and paid in 2021.

In January 2021, the Company issued and sold under the 2020 ATM an aggregate of 0.3 million common shares at an average price of $162.46 per share with aggregate proceeds of $46.7 million, which were net of equity issuance costs of $0.7 million. An additional $0.5 million of stamp taxes related to this amount was paid in 2021.

In January 2021, in connection with the August 2019 Sales Agreement, the Company filed a prospectus supplement with the SEC to offer and sell, from time to time, common shares having aggregate gross proceeds of up to $600.0 million. In July 2021, the Company filed a new prospectus supplement with the SEC, which replaced the previous prospectus supplement filed in January 2021, to offer and sell, from time to time, the common shares remaining under the original prospectus supplement having aggregate gross proceeds of up to $419.8 million, or, together with the January 2021 prospectus supplement, the 2021 ATM.

As of December 31, 2021, the Company issued and sold an aggregate of 1.1 million common shares under the 2021 ATM at an average price of $169.82 per share for aggregate proceeds of $177.8 million, which were net of equity issuance costs of $2.4 million. An additional $1.8 million of stamp taxes related to this amount was paid in 2021.

As of December 31, 2022, the Company has issued and sold an aggregate of 1.1 million common shares under the 2021 ATM at an average price of $168.79 per share for aggregate proceeds of $178.8 million, which were net of equity issuance costs of $2.4 million.

The Common Shares have the following characteristics:

Voting Rights

The holders of common shares are entitled to one vote for each common share held at all meetings of shareholders.

Dividends

The holders of common shares are entitled to receive dividends, if and when resolved upon by the general meeting of shareholders based on a respective proposal by the Board of Directors and provided that the Company disposes of sufficient freely distributable reserves. As of December 31, 2022, no dividends have been declared or paid since the Company's inception.

Liquidation

The holders of the common shares are entitled to share ratably in the Company's assets available for distribution to shareholders in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or upon the occurrence of a deemed liquidation event.

11. Equity-based Compensation

Option and Grant Plans

In April 2015, the Company's shareholders approved the 2015 Stock Option and Grant Plan, or the 2015 Plan, and in July 2016, the Company's shareholders approved the 2016 Stock Option and Incentive Plan, or the 2016 Plan. In May 2018, the Company's shareholders approved the 2018 Stock Option and Incentive Plan, or the 2018 Plan (collectively, the "Plans"). Subsequent to the IPO, no further options were granted under the 2015 Plan. The Plans provide for the issuance of equity awards in the form of restricted shares, options to purchase common shares which may constitute incentive stock options, or ISOs, or non-statutory stock options, or NSOs, unrestricted stock unit grants, and qualified performance and market-based awards to eligible employees, officers, directors, non-employee consultants and other key personnel. Terms of the equity awards, including vesting requirements, are determined by the Company's board of directors, subject to the provisions of the Plans. Options granted by the Company typically vest over four years and have a contractual life of ten years. Restricted stock unit grants typically vest over two to four years. At December 31, 2022, the Company had 26,705,365 common shares authorized for issuance under the 2018 Plan and 10,338,717 common shares available for future grant under the 2018 Plan.

Equity-Based Compensation Expense

The Company recognized stock-based compensation expense totaling $97.9 million, $102.4 million, and $66.0 million during the years ended December 31, 2022, 2021 and 2020, respectively. Stock-based compensation expense by classification within the consolidated statements of operations and comprehensive (loss) income is as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Research and development	$ 53,956	$ 59,683	$ 35,120
General and administrative	43,991	42,707	30,898
Total	$ 97,947	$ 102,390	$ 66,018

As of December 31, 2022, there was $107.9 million and $67.8 million of unrecognized compensation expense related to unvested stock options and restricted stock units, respectively, that is expected to be recognized over a weighted-average period of 2.4 and 2.3 years, respectively.

Stock Options

The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Years Ended December 31,		
	2022	2021	2020
Options granted	1,492,589	1,616,255	2,182,773
Weighted-average exercise price	$ 60.19	$ 124.32	$ 68.91
Weighted-average grant date fair value	$ 38.54	$ 77.38	$ 42.28
Assumptions:			
Expected volatility	70.2%	70.3%	69.2%
Expected term (in years)	6.0	6.0	6.0
Risk-free interest rate	2.6%	1.0%	0.6%
Expected dividend yield	0.0%	0.0%	0.0%

The following table summarizes stock option activity under the Company's equity award plans (intrinsic value in thousands):

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2021	7,812,982	$ 58.07	7.4	$ 219,103
Granted	1,492,589	60.19		
Exercised	(1,235,528)	29.66		
Cancelled or forfeited	(839,810)	85.13		
Outstanding at December 31, 2022	7,230,233	$ 60.22	7.0	$ 32,131
Exercisable at December 31, 2022	4,769,450	$ 51.76	6.2	$ 30,915
Vested and expected to vest at December 31, 2022	7,230,233	$ 60.22	7.0	$ 32,131

The total intrinsic value (the amount by which the fair market value exceeded the exercise price) of stock options exercised during the year ended December 31, 2022, 2021 and 2020 was $40.8 million, $119.5 million, and $104.2 million, respectively.

As of December 31, 2022, options to purchase 1,048,911 common shares subject to performance-based vesting conditions were vested, as performance conditions were satisfied in prior years, and there were 170,652 options to purchase common shares subject to performance-based vesting conditions outstanding. Activity related to stock options subject to performance-based vesting conditions is included in the table above.

As of December 31, 2022, options to purchase 150,000 common shares subject to market-based vesting conditions were vested, as market conditions were satisfied in prior years. 150,000 options to purchase common shares subject to market-based vesting conditions were outstanding as of December 31, 2022. Activity related to stock options subject to market-based vesting conditions is included in the table above.

The Company did not grant stock options subject to performance-based or market-based vesting conditions during 2022, 2021, and 2020.

Restricted Stock Units

The following table summarizes the restricted stock unit activity under the Company's equity award plans:

	Shares	Weighted-Average Grant Date Fair Value
Unvested balance at December 31, 2021	934,175	$ 100.14
Granted	853,326	62.31
Vested	(237,932)	83.88
Cancelled or forfeited	(224,384)	91.69
Unvested balance at December 31, 2022	1,325,185	$ 80.13

During the years ended December 31, 2022, 2021 and 2020, the total fair value of restricted stock units vested was $14.3 million, $45.3 million, and $21.6 million, respectively.

During 2022, the Company granted 150,000 performance stock units with market-based vesting conditions in which the recipient is eligible to receive between zero and 150,000 common shares at the end of a three-year service period based upon achieving a specified average stock price. Expense for these awards is being recognized over the requisite service period. As of December 31, 2022, 150,000 of the performance stock units were unvested. Activity related to stock units subject to market-based vesting conditions is included in the table above.

The Company did not grant stock units subject to performance-based or market-based vesting conditions during 2021 and 2020.

Award modifications

Equity award modifications for certain equity awards held by departing employees for the years ended December 31, 2022, 2021 and 2020 were not material to the Company's stock-based compensation expense.

Employee Stock Purchase Plan

On July 19, 2016, the Company's board of directors adopted its 2016 Employee Stock Purchase Plan, or the ESPP Plan, which was subsequently approved by its shareholders and became effective on October 19, 2016. The ESPP Plan authorizes the initial issuance of up to a total of 0.4 million shares of the Company's common stock to participating employees. The Company activated its ESPP Plan on January 1, 2020. The Company issued 36,559 and 21,590 shares under the ESPP Plan during the years ended December 31, 2022 and 2021, respectively.

12. Net (Loss) Income Per Share Attributable to Common Shareholders

Basic net (loss) income per share is calculated by dividing net (loss) income attributable to common shareholders by the weighted-average number of common shares outstanding during the period. Diluted net (loss) income per share is calculated by dividing the net (loss) income attributable to common shareholders by the weighted-average number of common share equivalents outstanding for the period, including any dilutive effect from outstanding stock options and warrants using the treasury stock method. The Company's net (loss) income is net (loss) income attributable to common shareholders for all periods presented.

The following table sets forth the computation of basic and diluted net (loss) income per share for the periods ended (in thousands, except share and per share amounts):

	Year ended December 31,		
	2022	2021	2020
Net (loss) income	$ (650,175)	$ 377,661	$ (348,865)
Basic weighted-average common shares outstanding	77,746,575	75,948,686	65,949,672
Effect of potentially dilutive securities:			
Outstanding options	—	3,990,579	—
Unvested restricted common shares	—	454,231	—
Diluted weighted-average common shares outstanding	77,746,575	80,393,496	65,949,672
Net (loss) income per common share — basic	$ (8.36)	$ 4.97	$ (5.29)
Net (loss) income per common share — diluted	$ (8.36)	$ 4.70	$ (5.29)

The Company did not include the securities in the following table in the computation of the net (loss) income per share calculations because the effect would have been anti-dilutive during each period:

	Year ended December 31,		
	2022	2021	2020
Outstanding options	7,230,233	1,765,881	8,101,980
Unvested restricted common shares	1,325,185	225,904	894,092
ESPP	19,105	6,671	11,257
Total	8,574,523	1,998,456	9,007,329

13. 401(k) Savings Plan

The Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan") in November 2016. The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pretax basis. The Company contributed $3.2 million, $3.4 million, and $1.9 million to the 401(k) Plan for the years ended December 31, 2022, 2021 and 2020, respectively.

14. Income Taxes

The Company is subject to U.S. federal and various state corporate income taxes as well as taxes in foreign jurisdictions for the foreign parent and where foreign subsidiaries have been established.

Net (loss) income before taxes

For the years ended December 31, 2022, 2021 and 2020, the (loss) income before provision for income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Domestic	$ 1,321	$ 4,569	$ 7,630
Foreign	(651,821)	374,962	(355,686)
Total	$ (650,500)	$ 379,531	$ (348,056)

The benefit from (provision for) income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Current income taxes:			
Federal	$ (444)	$ (80)	$ (248)
State	(241)	(42)	(151)
Foreign	—	—	(1)
Total current income taxes	(685)	(122)	(400)
Deferred income taxes:			
Federal	1,010	(1,748)	(409)
State	—	—	—
Foreign	—	—	—
Total deferred income taxes	1,010	(1,748)	(409)
Total income tax benefit (provision)	$ 325	$ (1,870)	$ (809)

A reconciliation of income tax expense computed at the statutory corporate income tax rate to the effective income tax rate for the years ended December 31, 2022, 2021 and 2020 is as follows:

	Years Ended December 31,		
	2022	2021	2020
Income tax expense at statutory rate	11.9%	11.9%	11.9%
State income tax, net of federal benefit	1.2%	(1.0)%	1.0%
Nondeductible expenses	(0.2)%	0.7%	0.1%
Foreign rate differential	(0.1)%	0.6%	(0.1%)
Statutory to US GAAP permanent differences	0.0%	0.0%	0.0%
Stock-based compensation	(0.2)%	(2.5%)	2.3%
Impact of deferred rate change	(0.1)%	0.0%	0.0%
Research credits	3.3%	(4.2)%	3.3%
Change in valuation allowance	(15.8)%	(5.0)%	(18.7%)
Effective income tax rate	—	0.5%	(0.2%)

The federal statutory rate reflects the Switzerland mixed company service rate.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following (in thousands):

	Years Ended December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 118,432	$ 47,190
Accruals and reserves	4,782	5,878
Operating lease liabilities	66,436	61,476
Other deferred tax assets	10,154	6,362
Stock-based compensation	18,034	14,042
Research credit	63,416	37,878
Total deferred tax assets	281,254	172,826
Less valuation allowance	(198,279)	(98,649)
Net deferred tax assets	82,975	74,177
Deferred tax liabilities:		
Depreciation	(41,206)	(28,579)
Operating lease assets	(42,678)	(47,521)
Intangible assets	(18)	(31)
Other deferred tax liabilities	(209)	(192)
Total deferred tax liabilities	(84,111)	(76,323)
Long term deferred taxes	$ (1,136)	$ (2,146)

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of worldwide operating losses, the Company has concluded that it is more-likely-than-not that the benefit of its U.S. and non-U.S. deferred tax assets will not be realized. Accordingly, as of December 31, 2022 and 2021, the Company has provided a full valuation allowance against its net deferred tax assets in Switzerland and the United Kingdom. The Company has also provided a valuation allowance against the U.S. deferred tax assets that cannot be realized by existing deferred tax liabilities based upon when they are scheduled to reverse. The valuation allowance increased by $99.6 million during 2022, which is primarily attributable to increase in net operating loss carryforwards as a result of current year net loss.

As of December 31, 2022, the Company had no available U.S. federal net operating loss carryforwards. As of December 31, 2022, the Company had available non-U.S. net operating loss carryforwards of $1,979.7 million of which $988.4 million relate to Switzerland, $988.4 million relate to the Canton of Zug, and $2.9 million relate to the Company's wholly-owned subsidiary in the United Kingdom. The net operating losses generated in Switzerland and the Canton of Zug begin to expire in 2027 and the net operating losses generated in the United Kingdom can be carried forward indefinitely.

As of December 31, 2022, the Company had U.S. domestic federal research and development credit carryforwards of $27.3 million that begin to expire in 2039 for federal purposes, which are net of uncertain tax positions of $13.9 million. As of December 31,

2022, the Company had U.S. domestic federal orphan drug credit carryforwards of $22.7 million which begin to expire in 2040 for federal purposes, which are net of uncertain tax positions of $9.8 million. As of December 31, 2022, the Company had U.S. domestic state research and development credit carryforwards of $16.9 million which begin to expire in 2035, which are net of uncertain tax positions of $10.9 million.

ASC 740 clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statement by prescribing the minimum recognition threshold and measurement of a tax position taken or expected to be taken in a tax return.

As of December 31, 2022, the Company had gross unrecognized tax benefits of $34.5 million of which $32.3 million would favorably impact the effective tax rate if recognized. The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022, 2021 and 2020, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss.

The aggregate changes in gross unrecognized tax benefits were as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Balance at beginning of year	$ 21,395	$ 11,967	$ 5,231
Increases for tax positions taken during current period	10,439	9,911	7,004
Increases for tax positions taken in prior periods	2,702	—	—
Decreases for tax positions taken during current period	—	—	—
Decreases for tax positions taken in prior periods	—	(483)	(268)
Balance at end of year	$ 34,536	$ 21,395	$ 11,967

The Company files income tax returns in the U.S. federal jurisdiction, Massachusetts, California and certain non-U.S. jurisdictions. The Company is subject to U.S. federal, Massachusetts, California and non-U.S. income tax examinations by authorities for tax years ending after December 31, 2018. Research credits generated in prior tax years that are closed for examination may still be adjusted upon future examination if they have or will be used in a future period. The Company is subject to income tax examinations by authorities in its non-U.S. jurisdictions for all years.

[THIS PAGE INTENTIONALLY LEFT BLANK]

[THIS PAGE INTENTIONALLY LEFT BLANK]

[THIS PAGE INTENTIONALLY LEFT BLANK]

BOARD OF DIRECTORS

Dr. Rodger Novak
Chairman, Founder & President

Dr. Samarth Kulkarni
Chief Executive Officer

Dr. Ali Behbahani
General Partner, New Enterprise Associates

Dr. Maria Fardis
Venture Partner, Frazier Life Sciences

Dr. H. Edward Fleming, Jr.
Executive Vice President, Enavate Sciences

Dr. Simeon J. George
Chief Executive Officer
SR One Capital Management, LP

John T. Greene
Executive Vice President and Chief Financial Officer, Discover Financial Services

Dr. Katherine A. High
Visiting Professor, Rockefeller University

Dr. Douglas A. Treco
Lead Independent Director
Chief Executive Officer and Chairman, Inozyme Pharma

EXECUTIVE COMMITTEE

Dr. Samarth Kulkarni
Chief Executive Officer

Dr. Rodger Novak
Founder & President

Dr. Raju Prasad
Chief Financial Officer

Dr. Phuong Khanh Morrow
Chief Medical Officer

James R. Kasinger
General Counsel

CORPORATE HEADQUARTERS

Baarerstrasse 14
6300 Zug
Switzerland

US OFFICES

105 West First Street
South Boston, MA 02127

455 Mission Bay Boulevard South
San Francisco, CA 94158

UK OFFICES

85 Tottenham Court Road
London
W1T 4QT

TRANSFER AGENT AND REGISTRAR

American Stock Transfer & Trust Company, LLC
6201 15th Avenue
Brooklyn, NY 11219
Phone: +1.800.937.5449
www.amstock.com

INDEPENDENT AUDITORS

Ernst & Young Ltd.
Basel, Switzerland
Boston, MA

LEGAL COUNSEL

Walder Wyss AG
Zurich, Switzerland

Goodwin Procter, LLP
Boston, MA

ANNUAL GENERAL MEETING

The Annual General Meeting of Shareholders will be **June 8, 2023** at 8:00 A.M. CET at the offices of Walder Wyss Ltd., Seefeldstrasse 123, 8008 Zurich, Switzerland.

INVESTOR INFORMATION

Copies of our annual reports on Form 10-K, proxy statements, quarterly reports on Form 10-Q, and current reports on Form 8-K are available to shareholders upon request without charge. Please visit our website at www.crisprtx.com, send requests by e-mail to ir@crisprtx.com or send a written request to:

CRISPR Therapeutics, Inc., 105 West First Street, South Boston, MA 02127, ATTN: Investor Relations

STOCK INFORMATION

Our common shares are traded on the Nasdaq Global Market under the symbol “CRSP”.

FORWARD LOOKING STATEMENTS

This annual report contains “forward-looking statements” which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. The forward-looking statements in this annual report do not constitute guarantees of future performance. Investors are cautioned that statements in this annual report that are not strictly historical statements, including, but not limited to, statements concerning: the status of preclinical studies and clinical trials, including the safety, efficacy and clinical progress of our product candidates, and expectations regarding pipeline products and programs; the therapeutic value, development, and commercial potential of CRISPR/Cas-9 gene editing technologies; the expected benefits of our collaborations and therapies; and the intellectual property protection of our technology and therapies. You are cautioned that forward-looking statements are inherently uncertain. Such forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from those anticipated, including, without limitation, the risks identified in our annual report on Form 10-K and our other filings with the Securities and Exchange Commission. We assume no obligation to update any forward-looking information contained in this annual report.

CRISPR Therapeutics AG
Baarerstrasse 14
6300 Zug
Switzerland

www.crisprtx.com