verve™
THERAPEUTICS

2022 ANNUAL REPORT

NASDAQ: VERV

DEAR SHAREHOLDERS

Despite the availability of a number of treatments, cardiovascular disease (CVD) continues to be the leading cause of death worldwide, afflicting hundreds of millions of people. In the U.S. alone, one person dies every 34 seconds because of a cardiac event. Managing cardiovascular disease is a tremendous strain on the healthcare system, and heart disease remains one of the most expensive health conditions to treat in the U.S.

As a cardiologist, I have seen the toll heart disease takes on patients and families, often impairing quality of life and robbing people of healthy futures. We are in urgent need of new approaches to treat, and potentially prevent, CVD.

Verve's vision is to protect the world from CVD. We are passionate in our pursuit of this vision, and we are committed to a journey of continuous scientific innovation to develop medicines for patients in need.

Atherosclerotic cardiovascular disease (ASCVD) is the most common form of CVD and is caused by high, cumulative, life-long exposure to blood cholesterol, which clogs arteries. This cholesterol is carried by three lipoproteins: low-density lipoprotein (LDL), triglyceride-rich lipoproteins (TRL) or lipoprotein (a), also known as Lp(a).
One of the most effective ways to treat ASCVD is to get levels of these lipoproteins down as low as possible, for as long as possible.

We refer to today's treatment paradigm as the "chronic care model," and it has become abundantly clear that this model is broken and leaves many patients without adequate care. In the U.S. alone:

> Studies have shown that only 50% of ASCVD patients are on a statin to lower LDL cholesterol (LDL-C) even though statins are the standard of care.
>
> Only 27% of patients being treated with statins are at LDL-C goal, as defined by the American Heart Association.

"Verve's vision is to protect the world from CVD. We are passionate in our pursuit of this vision, and we are committed to a journey of continuous scientific innovation to develop medicines for patients in need.

Sekar Kathiresan, M.D.
Co-founder and chief executive officer

Why is this? The chronic care model places a heavy burden on patients, providers and the healthcare system, requiring daily pills or intermittent injections administered over decades.

Since our founding in 2018, we have been driven to transform the way ASCVD is treated by developing once-and-done gene editing treatments, delivered through a single, intravenous infusion, to address the root causes of ASCVD.

Our lead product candidate, VERVE-101, is designed to permanently switch off a cholesterol-raising gene, called *PCSK9,* in the liver and durably lower LDL-C. VERVE-101 utilizes lipid nanoparticle (LNP) mediated delivery to target the liver and novel base editing technology to make a single base change at a specific site in the *PCSK9* gene. This single spelling change disrupts PCSK9 protein production and reduces PCSK9 level as well as LDL-C level in the blood. In non-human primates, a single treatment of VERVE-101 has been shown to reduce blood LDL-C up to 68%, with durability extending to beyond a year.

In 2022, Verve achieved a major milestone and moved VERVE-101 into the first-ever clinical trial of an *in vivo* gene editor for an ASCVD indication.

Our Phase 1b heart-1 clinical trial is focused on treating patients with a prevalent and life-threatening type of familial hypercholesterolemia (FH) known as heterozygous hypercholesterolemia (HeFH). HeFH is a morbid disease characterized by severely elevated blood levels of LDL-C and development of ASCVD at early ages.

Our heart-1 clinical trial is enrolling patients in New Zealand and the United Kingdom, and we are continuing to work with the U.S. Food and Drug Administration to be able to expand clinical investigation into the U.S. as well. Given that VERVE-101 is a first-of-its-kind medicine, the initial heart-1 clinical trial is designed to evaluate the safety of VERVE-101 in single, ascending dose-escalation cohorts, each enrolling a small number of high-risk HeFH patients with, in most cases, severe CVD. We plan to share initial safety and pharmacodynamic data from the four dose escalation cohorts in the second half of this year.

FH is an important indication to solve therapeutically but it is just the tip of the iceberg for Verve. We are committed to reaching as many patients with ASCVD as possible. For our PCSK9 program, this involves a stepwise expansion approach, with a goal of moving from high-risk, HeFH patients into the broader HeFH patient population, which accounts for over three million people in the U.S. and Europe, and ultimately, into the full spectrum of ASCVD, which impacts approximately 54 million people in the U.S. and Europe today.

Similar to our approach to targeting the *PCSK9* gene, we are also advancing our development candidate, VERVE-201, for another validated gene target – *ANGPTL3*. We are developing VERVE-201

to turn off the *ANGPTL3* gene in the liver to disrupt ANGPTL3 protein production, which can lead to reductions in LDL-C and triglyceride levels through a mechanism distinct from that of *PCSK9*. VERVE-201 is designed to be delivered to the liver using our internally developed GalNAc-LNP delivery system. We plan to develop VERVE-201 initially for the treatment of the rarer form of FH, known as homozygous FH (HoFH), as well as for people with refractory hypercholesterolemia, defined as people with ASCVD on oral therapy and/or a PCSK9 inhibitor who are not at LDL-C goal.

In our preclinical studies of VERVE-201, we observed substantial ANGPTL3 editing, as well as meaningful reductions in both LDL-C and triglyceride levels. Based on these data, we are conducting additional preclinical studies to support a regulatory filing for the initiation of clinical development of VERVE-201. We anticipate initiating a Phase 1b clinical trial in 2024.

Beyond our lead programs, we have an active research and discovery organization working to expand our pipeline through both in-house efforts and strategic collaborations. We are advancing a second PCSK9 program that leverages our GalNAc-LNP delivery technology, as well as a novel gene editing approach targeting Lp(a), a genetic marker that is known to correlate with a high-risk of ASCVD and cardiac-related events.

Our collaboration with Vertex on the development of an *in vivo* gene editing program targeting an undisclosed liver disease is progressing well, and our relationship with Beam Therapeutics remains strong. These collaborations further support our goal of reaching as many patients as we can with single-course gene editing medicines.

We have made significant progress to date, with several exciting milestones ahead, including the first human data from our heart-1 clinical trial.

I am humbled by the commitment from our team as we execute our mission to transform the care of CVD and make a meaningful impact on the lives of people in the world. For us to achieve this, we require the continued support of the patient and physician community. As ever, the entire Verve team is grateful to the patients, families, caregivers, and medical teams who partake in our clinical trials and make our work possible. We also would like to express our gratitude to our shareholders for your continued support and encouragement.

We look forward to the year ahead and keeping you apprised of our progress.

Sincerely,

Sekar Kathiresan, M.D.
Co-founder and CEO

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 001-40489

VERVE THERAPEUTICS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**82-4800132**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
201 Brookline Avenue, Suite 601 Boston, Massachusetts	**02215**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 603-0070

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 stock, par value $0.001 per share	VERV	Nasdaq Global Select 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 voting and non-voting common stock held by non-affiliates of the Registrant was $557.6 million based on the closing price of the registrant's common stock on Nasdaq as of June 30, 2022, the last business day of the registrant's most recently completed second quarter.

The number of shares of registrant's common stock outstanding as of February 27, 2023 was 61,833,265.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement that will be filed for the 2023 Annual Meeting of Stockholders which the registrant intends to file with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2022, are incorporated by reference in Part III of this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K includes forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "contemplate," "continue" "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "will," "would," or the negative of these words or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the initiation, timing, progress and results of our research and development programs, preclinical studies and clinical trials, including the timing of our submissions of investigational new drug, or IND, applications, and clinical trial applications to regulatory authorities;
- the timing and conduct of our heart-1 clinical trial, an ongoing Phase 1b clinical trial of VERVE-101, including statements regarding the timing of enrollment and completion of the clinical trials and the period during which the data from clinical trials will become available;
- our expectations related to the hold that the U.S. Food and Drug Administration, or FDA, placed on our IND application to conduct a clinical trial evaluating VERVE-101 in the United States, including our plans and expectations for responding to the FDA;
- our estimates regarding expenses, future revenue, capital requirements, need for additional financing and the period over which we believe our existing cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements;
- the timing of and our ability to submit applications for and obtain and maintain regulatory approvals for our current and future product candidates;
- the potential therapeutic attributes and advantages of our current and future product candidates;
- our expectations about the translatability of results from studies in non-human primates into clinical trials in humans;
- our plans to develop and, if approved, subsequently commercialize any product candidates we may develop;
- the rate and degree of market acceptance and clinical utility of our products, if approved;
- our estimates regarding the addressable patient population and potential market opportunity for our current and future product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our expectations regarding our ability to obtain and maintain intellectual property protection;
- our ability to identify additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- the impact of government laws and regulations;
- our competitive position and expectations regarding developments and projections relating to our competitors and any competing therapies that are or become available;
- developments relating to our competitors and our industry;
- our ability to establish and maintain collaborations, including our collaborations with Beam Therapeutics, Inc. and Vertex Pharmaceuticals Incorporated;
- the impact of the COVID-19 pandemic and of global economic developments, including rising inflation and interest rates, on our business, operations, strategy and goals; and
- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We

have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, 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 reference in this Annual Report on Form 10-K and have filed as exhibits to our other filings with the Securities and Exchange Commission completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Except where the context otherwise requires or where otherwise indicated, the terms “we,” “us,” “our,” “our company,” “the company,” and “our business” in this Annual Report refer to Verve Therapeutics, Inc. and its consolidated subsidiary.

RISK FACTOR SUMMARY

Our business is subject to a number of risks of which you should be aware before making an investment decision. Below we summarize what we believe to be the principal risks facing our business, in addition to the risks described more fully in Item 1A, "Risk Factors" of Part I of this Annual Report on Form 10-K and other information included in this report. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations.

If any of the following risks occurs, our business, financial condition and results of operations and future growth prospects could be materially and adversely affected, and the actual outcomes of matters as to which forward-looking statements are made in this report could be materially different from those anticipated in such forward-looking statements:

- We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts;
- Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability;
- We are very early in our development efforts, and we only recently initiated our first clinical trial of a product candidate, VERVE-101, our product candidate targeting PCSK9. As a result, we expect it will be many years before we commercialize any product candidate, if ever. If we are unable to advance our current or future product candidates into and through clinical trials, obtain marketing approval and ultimately commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed;
- The U.S. Food and Drug Administration has placed the investigational new drug, or IND, application to conduct a clinical trial evaluating VERVE-101 in the United States on hold and the IND remains on hold. We cannot be certain that the hold will be lifted on a timely basis, or at all, and we may not be able to initiate our clinical trial of VERVE-101 in the United States;
- Gene editing, including base editing, is a novel technology in a rapidly evolving field that is not yet clinically validated as being safe and efficacious for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics are unproven and may never lead to marketable products. We are focusing our research and development efforts for VERVE-101 and VERVE-201, our development candidate targeting ANGPTL3, on gene editing using base editing technology, but other gene editing technologies may be discovered that provide significant advantages over base editing and we may not be able to access or use those technologies, which could materially harm our business;
- We are seeking to discover and develop new gene editing technologies and may not be successful in doing so;
- The outcome of preclinical studies and earlier-stage clinical trials may not be predictive of future results or the success of later preclinical studies and clinical trials and interim or preliminary data from our clinical trials may materially change as participant enrollment continues and more participant data become available;
- If any of the product candidates we may develop, or the delivery modes we rely on to administer them, including lipid nanoparticles, cause serious adverse events, undesirable side effects or unexpected characteristics, such events, side effects or characteristics could delay or prevent regulatory approval of the product candidates, limit the commercial potential or result in significant negative consequences following any potential marketing approval;
- Adverse public perception of genetic medicines, and gene editing and base editing in particular, may negatively impact regulatory approval of, and/or demand for, our potential products;
- Genetic medicines are complex and difficult to manufacture. We could experience delays in satisfying regulatory authorities or production problems that result in delays in our development programs, limit the supply of our product candidates we may develop, or otherwise harm our business;
- We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily;
- We have entered into collaborations, and may enter into additional collaborations, with third parties for the research, development, manufacture and commercialization of programs or product candidates. If these collaborations are not successful, our business could be adversely affected;

- If we or our licensors are unable to obtain, maintain, defend and enforce patent rights that cover our gene editing technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected;
- If we fail to comply with our obligations in our intellectual property license arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business;
- The intellectual property landscape around genome editing technology, including base editing, is highly dynamic, and third parties may initiate legal proceedings alleging that we are infringing, misappropriating, or otherwise violating their intellectual property rights, the outcome of which would be uncertain and may prevent, delay or otherwise interfere with our product discovery, development and commercialization efforts; and
- We face substantial competition, which may result in others discovering, developing or commercializing products before us or more successfully than we do. The market with respect to new products for the treatment of cardiovascular disease, for which the standard of care is well-established, is particularly competitive.

PART I

Item 1. Business.

Overview

We are a clinical-stage genetic medicines company pioneering a new approach to the care of cardiovascular disease, or CVD, transforming treatment from chronic management to single-course gene editing medicines. Despite advances in treatment over the last 50 years, CVD remains the leading cause of death worldwide. The current paradigm of chronic care is fragile—requiring rigorous patient adherence, extensive healthcare infrastructure and regular healthcare access—and leaves many patients without adequate care. Our goal is to disrupt the chronic care model for CVD by providing a new therapeutic approach with single-course *in vivo* gene editing treatments focused on addressing the root causes of this highly prevalent and life-threatening disease. Our initial two programs target PCSK9 and ANGPTL3, respectively, genes that have been extensively validated as targets for lowering blood lipids, such as low-density lipoprotein cholesterol, or LDL-C. We believe that editing these genes could potently and durably lower LDL-C throughout the lifetime of patients with or at risk for atherosclerotic cardiovascular disease, or ASCVD, the most common form of CVD.

Our approach leverages multiple breakthroughs in 21st century biomedicine—human genetic analysis, gene editing, messenger RNA, or mRNA, -based therapies and lipid nanoparticle, or LNP, delivery—to target genes that are predominantly expressed in the liver and disrupt the production of proteins that cause CVD. We are advancing a pipeline of single-course *in vivo* gene editing programs, each designed to mimic natural disease resistance mutations and turn off specific genes in order to lower blood lipids, thereby reducing the risk of ASCVD. We intend to initially develop these programs for the treatment of patients with familial hypercholesterolemia, or FH, a genetic disease that causes life-long severely elevated blood LDL-C, leading to increased risk of early-onset ASCVD. If our programs are successful in FH, we believe they could also provide a potential treatment for the broader population of patients with established ASCVD. Ultimately, we believe that these treatments could potentially be developed for administration to people at risk for ASCVD as a preventative measure similar to the way that certain vaccines offer long-term protection against infectious diseases.

High cumulative life-long exposure to LDL-C drives the development of atherosclerotic plaque that results in the hardening of arteries seen in ASCVD. The relationship between lowering of cumulative LDL-C exposure and reduction in the risk of ASCVD is among the best understood relationships in medicine. Studies have shown that lowering LDL-C by 39 mg/dL for five years in patients with established ASCVD reduces the risk of a further event by 21%, whereas a similar degree of LDL-C difference over a lifetime reduces the risk of a first ASCVD event by 88%. This demonstrates that the challenge is not only to substantially reduce LDL-C but also to sustain such a reduction throughout a patient's lifetime. We believe that the cornerstone of the treatment and prevention of ASCVD must be early and aggressive reduction of LDL-C for as long as possible.

The current standard of care is a chronic care model that often fails to sufficiently control overall LDL-C exposure due to the continuous and life-long nature of its treatment approaches and the inherent adherence issues it presents. As a result, a large proportion of patients with established ASCVD have LDL-C levels above the goal recommended by the American Heart Association, or the AHA, and the American College of Cardiology, or the ACC, leaving them at risk for recurrent ASCVD events and the potential for invasive medical procedures or even death. Furthermore, given the silent nature of the damage done by elevated LDL-C, many patients at risk for ASCVD do not properly appreciate the therapeutic benefits of consistent treatment as well as the substantial risk of foregoing treatment, focusing instead on the heavy, life-long medication burden of daily pills, lifestyle changes and other chronic approaches. We believe that single-course gene editing treatments that potently and durably control cumulative LDL-C exposure could fundamentally disrupt the chronic care model for treating patients with or at risk for ASCVD and relieve the significant burden placed on patients, providers and the healthcare system.

Our lead product candidate, VERVE-101, is designed to permanently turn off the PCSK9 gene in the liver. PCSK9 is a highly validated target that plays a critical role in controlling blood LDL-C through its regulation of the LDL receptor, or LDLR. Reduction of PCSK9 protein in the blood improves the ability of the liver to clear LDL-C from the blood. VERVE-101 utilizes LNP-mediated delivery to target the liver and base editing technology to make a single base change at a specific site in the PCSK9 gene in order to disrupt PCSK9 protein production.

In an *in vivo* proof-of-concept study of a precursor formulation of VERVE-101 in non-human primates, or NHPs, we observed substantial lowering of LDL-C levels that was sustained over an extended period of time following

treatment. In this study, following a single intravenous infusion of a base editor targeting PCSK9, we observed an average reduction of blood PCSK9 protein of 89% accompanied by an average reduction of blood LDL-C levels of 59% at two weeks after treatment. This LDL-C reduction was maintained at an average of 71% for two years following treatment.

In an ongoing preclinical study with VERVE-101 in NHPs, we observed 70% mean editing following a single administration of 1.5 mg/kg dose at the PCSK9 target gene site in liver biopsies taken at day 15. In this study, we also observed an average reduction in blood PCSK9 protein of 79% accompanied by an average reduction of blood LDL-C levels of 62% at two weeks after treatment. These reductions were durable when assessed for one year after treatment, with mean reduction in blood PCSK9 protein of 89% and blood LDL-C levels of 68%.

In addition, in our preclinical studies in NHPs, VERVE-101 has been well tolerated following a single administration with only mild elevations in liver function tests that resolved within two weeks. In primary human hepatocytes treated with VERVE-101, we observed on-target editing at the PCSK9 target site and did not observe significant editing at any of approximately 3,000 identified potential off-target sites.

Based on our preclinical data, we are advancing VERVE-101 initially for the treatment of heterozygous familial hypercholesterolemia, or HeFH. We plan to expand clinical development of VERVE-101 in a stepwise fashion beyond HeFH for the treatment of patients with established ASCVD, who are not at LDL-C goal on oral therapy, which represents hundreds of millions of potential patients globally. Ultimately, we believe that VERVE-101 may be useful to people at risk for ASCVD as a preventative measure in the general population.

The heart-1 trial is designed to enroll approximately 40 adult patients with HeFH who have established ASCVD and evaluate the safety and tolerability of VERVE-101 administration, with additional analyses for pharmacokinetics and reductions in blood PCSK9 protein and LDL-C. The trial includes three parts – (A) a single ascending dose portion, followed by (B) an expansion single-dose cohort, in which additional participants will receive the selected potentially therapeutic dose and (C) an optional second-dose cohort, in which eligible participants in lower dose cohorts in Part A have the option to receive a second treatment at the selected potentially therapeutic dose. During our interactions with regulators in New Zealand and the United Kingdom, country-specific protocols have been developed to account for various modifications to eligibility, design, and conduct in each country.

We have received clearance of our clinical trial applications, or CTAs, for VERVE-101 in New Zealand and the United Kingdom, and in July 2022, we announced that the first patient had been dosed with VERVE-101 in our heart-1 clinical trial. In November 2022, we announced that we completed dosing of VERVE-101 in the first dose cohort of the dose-escalation portion of the heart-1 clinical trial, a global Phase 1b open-label clinical trial. Enrollment efforts are ongoing in New Zealand and the United Kingdom. We plan to report initial safety and pharmacodynamic data from the dose-escalation portion of the heart-1 clinical trial in the second half of 2023.

We submitted our investigational new drug, or IND, application to conduct a clinical trial evaluating VERVE-101 in patients with HeFH to the U.S. Food and Drug Administration, or FDA, in October 2022 and were subsequently informed by the FDA that our IND application was placed on hold. In December 2022, we received a clinical hold letter from the FDA that outlined the information required to resolve the hold, including additional preclinical data relating to: (i) potency differences between human and non-human cells, (ii) risks of germline editing, and (iii) off-target analyses on non-hepatocyte cell types. Clinical data from the ongoing heart-1 clinical trial in New Zealand and the U.K. were not included in the IND application package submitted to the FDA. In the clinical hold letter, the FDA requested available clinical data from the trial. In addition, the FDA has requested that we modify the trial protocol in the United States to incorporate additional contraceptive measures and to increase the length of the staggering interval between dosing of participants. We intend to submit our response to the FDA as expeditiously as possible.

VERVE-201, our development candidate targeting ANGPTL3,is designed to permanently turn off the ANGPTL3 gene in the liver. ANGPTL3 is a key regulator of cholesterol and triglyceride metabolism. We believe that disrupting ANGPTL3 protein production may lead to reductions in LDL-C and triglyceride levels through a mechanism distinct from that of PCSK9. We plan to develop this program for the treatment of homozygous familial hypercholesterolemia, or HoFH, which affects approximately 1,300 people in the United States, as well as for refractory hypercholesterolemia defined as people with ASCVD who are not at LDL-C goal on oral therapy and a PCSK9 inhibitor. Ultimately, we believe that VERVE-201 may also be useful to people at risk for ASCVD as a preventative measure in the general population. We are conducting preclinical studies to support a regulatory filing for the initiation of clinical development of VERVE-201 and anticipate initiating a Phase 1b clinical trial in 2024.

For VERVE-201, we plan to utilize internally developed GalNAc-LNP to deliver a base editor targeting the ANGPTL3 gene to the liver. In patients with HoFH, delivery of base editors with standard LNPs to the liver is challenging due to the deficiency of LDLR, which is known to mediate LNP uptake. We have developed proprietary LNPs with a GalNAc ligand designed to bind to asialoglycoprotein receptors, or ASGPR, in the liver, which bypass LDLR, thereby enabling uptake into the liver in HoFH patients.

In our preclinical studies of a precursor formulation of VERVE-201 we used a single treatment of two different formulations of our proprietary GalNAc-LNPs to deliver an ANGPTL3-targeted base editor. We observed approximately 94% (n=3) and 97% (n=3) reduction in blood ANGPTL3 protein, and reductions in LDL-C of nearly 100 mg/dL, which was an approximately 35% reduction from baseline. We conducted these studies in an internally developed NHP model of HoFH, which we created by editing the LDLR gene in wild-type NHPs and eliminating LDLR expression in the livers of NHPs using a Cas9 and dual guide RNA strategy encapsulated in standard LNPs. In this model, we achieved nearly 70% whole liver DNA editing at the LDLR gene, resulting in an approximately 94% reduction in LDLR protein in the liver and a six-fold increase in blood LDL-C.

In a proof of concept study of an ANGPTL3 base editor in NHPs (n=4), we observed an approximate 96% reduction in blood ANGPTL3 protein from baseline, with follow-up out to two years. In addition, no long-term impacts were observed on markers of liver toxicity, as measured by alanine aminotransferase and bilirubin levels following treatment administration.

We have also assessed the potential broad utility of our proprietary GalNAc-LNP approach for delivery of an ANGPTL3-targeted base editor, in a preclinical study evaluating delivery efficiency of our ANGPTL3 base editor using either a GalNAc-LNP or a standard LNP without GalNAc in wild-type NHPs with normal livers. In these studies, we observed that wild-type NHPs treated with our ANGPTL3-targeted base editor delivered via our GalNAc-LNP had an approximately 89% reduction in ANGPTL3 protein compared to an approximately 74% reduction in wild-type NHPs treated with a standard LNP.

We are continuing to invest and build out capabilities in the development of novel and optimized GalNAc-targeting ligands, optimal lipid anchors, optimal compositions and ratios of LNP components, and optimal processes of addition and LNP formation with targeting ligands. We believe GalNAc provides a delivery platform for patients with both forms of FH and potentially may be applicable in other applications where liver-directed delivery is advantageous. We have also generated data where we observed that the GalNac-LNP can efficiently deliver base editors targeting PCSK9 as well. In this study, we observed approximately 87% reduction in blood PCSK9 protein after delivering a base editor targeting PCSK9 using GalNac-PCSK9 LNPs in wild-type NHPs. We believe this data suggests that GalNAc-LNP delivery may have broad utility for liver editing in other indications and are advancing a GalNAc-LNP delivered PCSK9 base editor into preclinical development.

We are focused on building the preeminent company developing gene editing medicines to treat patients with CVD, the world's leading cause of mortality. We intend to leverage the expertise and capabilities of our team to expand our pipeline beyond PCSK9 and ANGPTL3 and apply our single-course gene editing approach to additional *in vivo* liver gene editing treatments, such as our program targeting lipoprotein(a), or Lp(a), to develop a suite of single-course gene editing medicines that address the root causes of disease.

Our team

We were founded in 2018 by a team of world-renowned researchers in cardiovascular genetics, pioneers of gene editing and proven business leaders, including Sekar Kathiresan, M.D., Kiran Musunuru, M.D., Ph.D., MPH, J. Keith Joung, M.D., Ph.D., Burt Adelman, M.D., Issi Rozen, MBA, and Barry Ticho, M.D., Ph.D. Since our founding, we have built an organization and culture driven by a talented team of individuals who embody the meaning behind our name—vigor, spirit and enthusiasm—and who are motivated by a common goal of transforming the care of patients with or at risk for CVD.

Members of our leadership team have extensive collective experience in human genetics, gene editing, CVD care and drug development and commercialization. Our chief executive officer, Dr. Kathiresan, is a preventive cardiologist who has made groundbreaking discoveries of genetic mutations that confer resistance to CVD. Andrew Ashe, J.D., our president, chief operating officer and general counsel, is an accomplished biotech executive with over 20 years of experience in operations and legal management. Andrew Bellinger, M.D., Ph.D., our chief scientific officer and chief medical officer, is a cardiologist with proven expertise in drug delivery, drug development and translational medicine. Allison Dorval, our chief financial officer, has more than 20 years of leadership in finance, accounting, financial reporting and investor relations. Joan Nickerson, our Chief Adminstrative Officer, has over 25 years of experience in human resources.

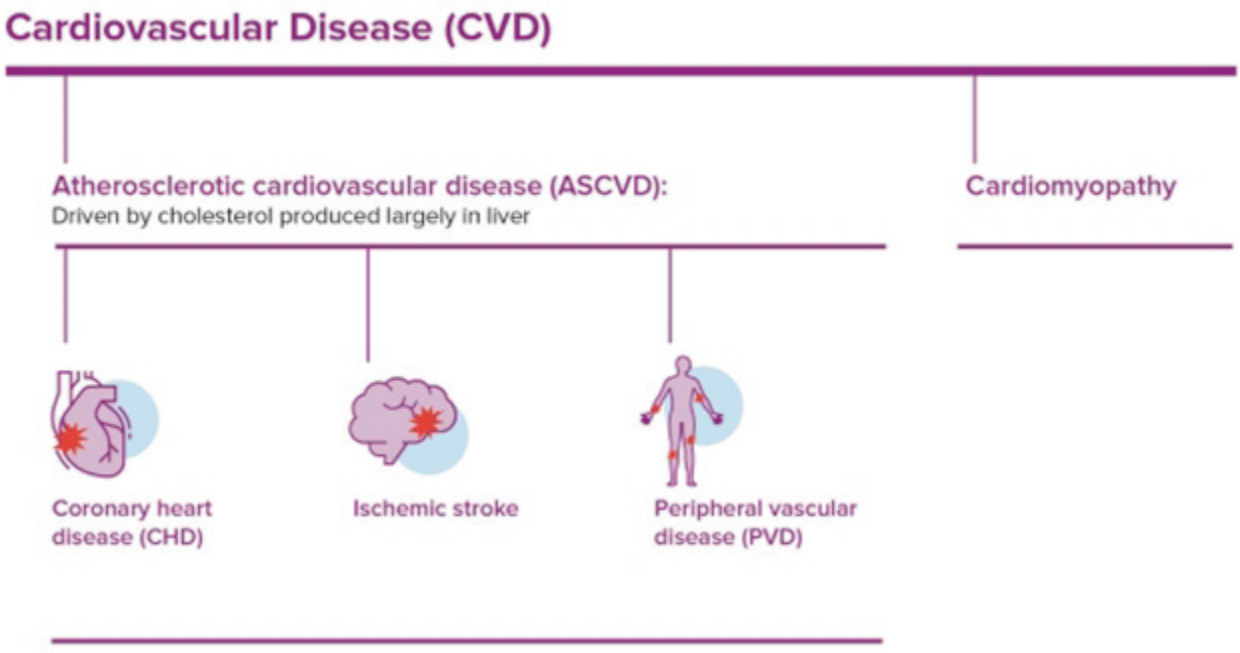
We have a Scientific Advisory Board, or SAB, comprising leading experts in the fields of cardiology, human genetics, translational medicine, delivery technologies, business and finance, including Eugene Braunwald, M.D., Daniel J. Rader, M.D., Andrew Geall, Ph.D., Anthony Philippakis, M.D., Ph.D, Kiran Musunuru, M.D., Ph.D., MPH, and Penny M. Heaton, M.D. Dr. Braunwald, a cardiovascular medicine specialist at Brigham and Women's Hospital and Hersey Professor of Medicine at Harvard Medical School, serves as chair of our SAB, has been listed as the most frequently cited author in cardiology, and was the first cardiologist elected to the National Academy of Sciences.

We have in-licensed technologies and intellectual property covering various elements of gene editing, including base editing and CRISPR nucleases, as well as multiple LNPs, with licenses from Beam Therapeutics Inc., or Beam, The Broad Institute, Inc., or Broad, Editas Medicine, Inc., the President and Fellows of Harvard College, or Harvard, Massachusetts General Hospital, Acuitas Therapeutics Inc., or Acuitas, and Novartis Pharma AG, or Novartis.

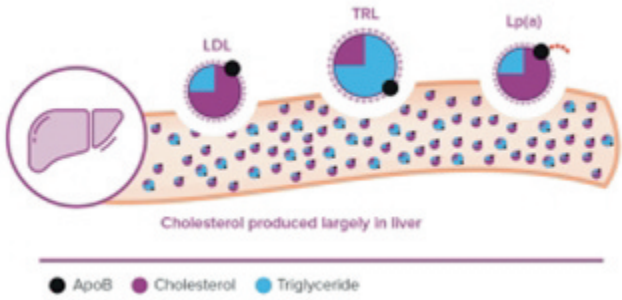
Transforming cardiovascular care

Despite advances in treatment over the last 50 years, CVD remains a global epidemic. The current paradigm of chronic care is fragile—requiring rigorous patient adherence, extensive healthcare infrastructure and regular healthcare access—and leaves many patients without adequate care. CVD remains the leading cause of death worldwide, responsible for nearly one in three deaths according to the World Health Organization. It is also a leading contributor to reductions in life expectancy and is one of the most expensive health conditions in the United States. According to the United States Centers for Disease Control and Prevention, or CDC, CVD costs the U.S. healthcare system more than $350 billion per year in annual costs and lost productivity. Our goal is to disrupt the chronic care model for CVD by providing a new therapeutic approach focused on addressing the root causes of this highly prevalent and life-threatening disease.

CVD collectively refers to diseases of the heart and blood vessels, which are diagnosed as ASCVD, among others, as depicted in the figure below. In ASCVD, a large subset of CVD, cholesterol drives the development of atherosclerotic plaque, a mixture of cholesterol, cells and cellular debris in the wall of a blood vessel that results in the hardening of the arteries.



High cumulative life-long exposure to blood cholesterol, which is carried in each of low-density lipoprotein, or LDL, triglyceride-rich lipoprotein, or TRL, or Lp(a), is a root cause of ASCVD. The graphic below depicts these liver-produced lipoproteins being secreted into the blood and their typical compositions, comprising cholesterol and triglycerides and with apolipoprotein B, or ApoB, on the surface. Each of these three lipoproteins represents an independent pathway of risk for ASCVD, and we believe that concurrently reducing the blood lipids carried in more than one of these pathways should provide additive benefit for the treatment of ASCVD.



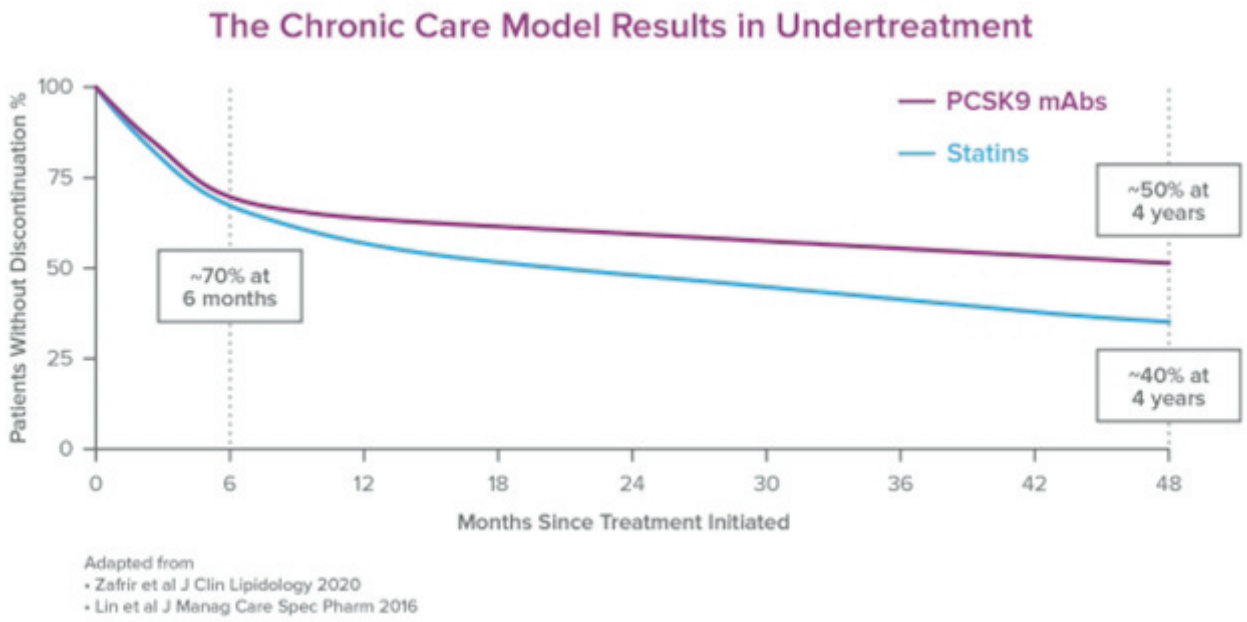
Current treatment approaches to lower LDL-C utilize continuous, life-long treatment, and due to the limitations of this chronic care model, cumulative exposure to LDL-C for many patients with ASCVD remains insufficiently controlled. The most common treatment for patients with ASCVD is daily statin pills in combination with recommended therapeutic lifestyle changes. There are several non-statin daily pills, including ezetimibe, bile acid sequestrants and bempedoic acid, that may be used alone or added sequentially to statin treatment in order to help patients with ASCVD reach recommended LDL-C goals. There are also two FDA-approved monoclonal antibodies, or mAbs, evolocumab and alirocumab, that target and bind to PCSK9 protein and are typically administered via injection twice per month. In addition, inclisiran, a small interfering RNA, or siRNA, that targets PCSK9 and is subcutaneously administered twice per year, was approved by the FDA and the European Medicines Administration, or EMA. Despite these approved treatments, effectively controlling LDL-C levels long-term in patients with or at high risk for ASCVD remains a significant unmet need.

The relationship between lowering of cumulative LDL-C exposure and reduction in the risk of ASCVD is among the best understood relationships in medicine. Human genetic studies have shown that those with FH, a genetic disease, have life-long severely elevated blood LDL-C, which can lead to increased risk of early-onset ASCVD. Conversely, individuals born with resistance mutations that turn off a cholesterol-raising gene expressed in the liver, such as PCSK9, have life-long low levels of LDL-C and rarely suffer from ASCVD. These insights point to the importance of early aggressive treatment to reduce LDL-C exposure over a patient's lifetime. For patients with established ASCVD, such as those who have previously suffered a heart attack, clinical treatment guidelines published by the AHA/ACC recommend lowering blood LDL-C to a goal of less than 70 mg/dL, and the European Society of Cardiology, or ESC, recommends lowering blood LDL-C to a goal of less than 55 mg/dL. If blood LDL-C is maintained low enough for long enough, the risk of a first ASCVD event, including a heart attack, can be dramatically reduced. Studies have shown that lowering LDL-C by 39 mg/dL for five years in patients with established ASCVD reduces the risk of a further event by 21%, whereas a similar degree of LDL-C difference over a lifetime reduces the risk of a first ASCVD event by up to 88%.

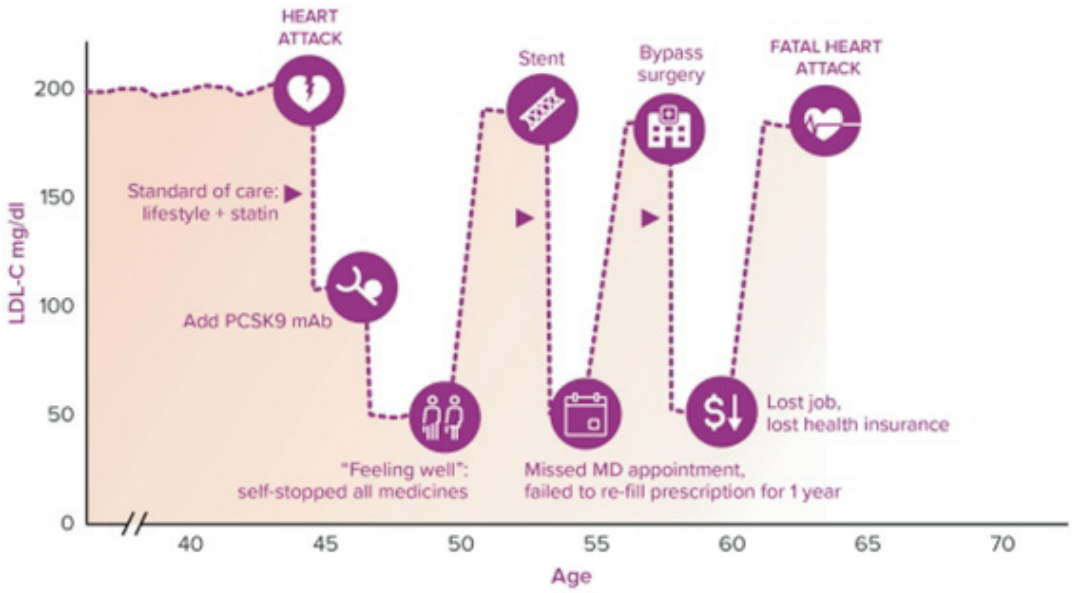
Despite the availability of statin and non-statin therapies, cumulative exposure to LDL-C is often insufficiently controlled in many patients with ASCVD. As a result, a large proportion of patients with established ASCVD have LDL-C levels above clinical treatment guidelines. In a national registry of outpatient cardiovascular care in the United States, out of 2.6 million patients who had suffered a clinical ASCVD event, 53% had not received any cholesterol-lowering therapy and 72% remained above the LDL-C levels recommended by the AHA/ACC. Further, data from a clinical trial of approximately 6,000 patients in the year following a heart attack showed that among the approximately 3,000 patients for whom the medication was provided for free, only 39% reported full adherence to their statin therapy.

A large proportion of patients with or at risk for ASCVD opt against starting or remaining on treatment due to the heavy, life-long medication burden associated with daily pills or frequent injections. Given the silent nature of the damage done by elevated LDL-C, many patients at risk for ASCVD do not properly appreciate the therapeutic benefits of consistent treatment as well as the substantial risk of foregoing treatment, focusing instead on the heavy, life-long medication burden of chronic approaches. Numerous prior studies of statins and injectable mAb PCSK9 inhibitors showed that treatment discontinuation is frequent. The graphic below illustrates findings from

two of these studies, which showed that 50% of patients or fewer remain on treatment with PCSK9 inhibitor mAbs or statins over four years.



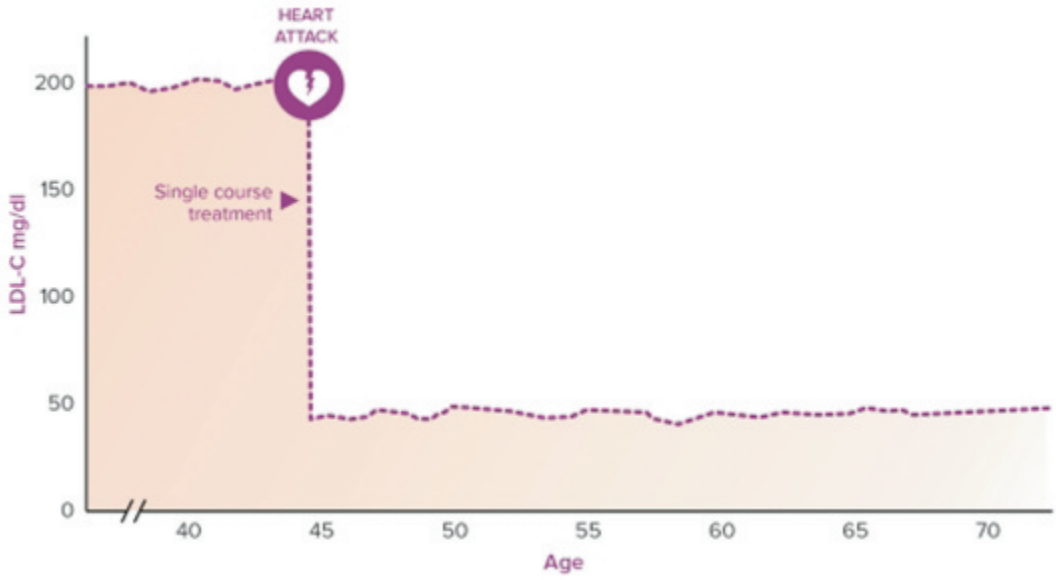
Incomplete adherence to treatment may result in significant oscillation in blood LDL-C levels over a patient's lifetime. The illustrative graphic below depicts the journey of a hypothetical patient with FH who began standard-of-care treatment after suffering a heart attack at age 44, at which point the patient was diagnosed with ASCVD, and the potential consequences of incomplete control of LDL-C over several years due to poor adherence and insufficient healthcare access. Incomplete LDL-C control can lead to recurrent clinical ASCVD events and the need for invasive medical procedures, such as intracoronary stenting and coronary artery bypass surgery, and can be fatal. These recurrent events and procedures place a heavy burden on patients, treating providers and the medical system as a whole, with increased cost and use of healthcare services.



Advantages of our single-course gene editing treatments for ASCVD

We believe that single-course gene editing treatments for patients with ASCVD have the potential to solve many of the challenges of the chronic care model and create a new paradigm for the treatment of this highly prevalent

and life-threatening disease. By potently and durably controlling cumulative LDL-C exposure throughout a patient's lifetime, we believe our gene editing medicines could fundamentally disrupt the chronic care model for patients with or at risk for ASCVD and relieve the significant burden placed on patients, providers and the healthcare system. The illustrative graphic below depicts the journey of the same hypothetical patient with FH who, in this case, received a single-course gene editing treatment after suffering a heart attack and avoided recurrent ASCVD events as a result.



To achieve our goal of transforming the treatment of ASCVD, we are developing a pipeline of single-course gene editing treatments that leverage multiple breakthroughs of 21st century biomedicine—human genetic analysis, gene editing, mRNA-based therapies and LNP-mediated delivery. We believe our approach benefits from the following potential advantages:

- *Validated liver targets implicated in ASCVD risk:* Our approach specifically targets genes that are predominantly expressed in the liver and have been validated through human genetics research. Naturally occurring mutations in each of these target genes are associated with a reduced risk of ASCVD. Our gene editing programs are designed to mimic these natural resistance mutations to turn off specific genes in the liver implicated in the risks of ASCVD. Such resistance mutations in PCSK9, even in adults with homozygous mutations and complete PCSK9 protein deficiency, do not appear to have any serious adverse health consequences. Furthermore, there is established human pharmacologic proof-of-concept and positive tolerability profiles with other modalities targeting these genes, such as mAbs, siRNA and antisense oligonucleotides.
- *Potent, durable and life-long lowering of blood lipids through a single-course treatment:* We are leveraging gene editing technologies, including base editing, to make a permanent change in the target gene and disrupt the production of specific proteins that cause ASCVD. The durability of a gene editing approach appears to hold true in tissues with cell turnover, such as the liver, since the edit is passed on as cells divide. With VERVE-101, we are leveraging base editing with the goal of potently and permanently reducing blood lipids in order to create the potential for a life-long therapeutic outcome. In a preclinical proof-of-concept study in NHPs using a precursor formulation of VERVE-101, we observed a 59% reduction in blood LDL-C at two weeks after treatment, with LDL-C reduction maintained at an average of 71% at two years. In another preclinical proof-of-concept study in NHPs, we observed that a single administration of a precursor formulation of VERVE-201 targeting ANGPTL3 resulted in a 64% reduction in blood triglycerides at two weeks after treatment, with triglyceride reduction maintained at an average of 69% at ten months. We believe that our gene editing approach has the potential to potently and durably lower blood lipids throughout a patient's lifetime, thereby reducing their risk of ASCVD.
- *Designed and optimized to reduce or avoid safety risks:* To optimize the safety profile of our gene editing programs, we utilize non-viral LNP delivery of a gene editor to the liver due to the potentially superior safety profile of LNPs compared with available viral delivery approaches, specifically the minimization of genome integration risk and immunogenicity. In addition, we use base editing for our initial programs, which enables

highly precise editing at the single base pair level and minimizes the risks of unwanted DNA modifications associated with double-stranded breaks from nuclease-based editing approaches. Finally, we extensively screen pairs of gene editors with guide RNA, or gRNA, in human cells, mice and NHPs to maximize the likelihood that our gene editing programs will have limited or no off-target editing effects. For VERVE-101, we have identified a base editor paired with a gRNA targeting PCSK9 and have not observed any significant off-target editing in preclinical studies using primary human hepatocytes.

- *A suite of complementary single-course gene editing treatments to broadly reduce blood lipids and ASCVD risk:* We are focused on targeting distinct pathways implicated in elevated blood lipid levels and related ASCVD risk. VERVE-101, our lead program, is designed to target the PCSK9 gene, a validated regulator of blood LDL-C levels. VERVE-201 is designed to target the ANGPTL3 gene, a regulator of both cholesterol and triglycerides that contributes to ASCVD risk independent of the PCSK9 pathway. We believe that patients with refractory hypercholesterolemia may benefit from treatment with VERVE-201.
- *Potential to manufacture our programs in a scalable manner to reach a broad population:* We have designed our single-course treatments as LNPs encapsulating mRNA and gRNA, a similar construction to that used in mRNA-based vaccines approved by the FDA for the prevention of COVID-19. We believe we will benefit from the rapid increase in investment, validation and real-world application of these technologies on a global scale as a result of the COVID-19 pandemic, which should enhance our potential to manufacture our gene editing programs for use with a broad patient population. We believe that scalable manufacturing is paramount to unlocking the true potential of our single-course gene editing treatments to tackle the worldwide burden of ASCVD.

Our strategy

We are executing a strategy with the following key elements:

- *Employ a stepwise approach to realize the full potential of VERVE-101and VERVE-201.* We are pioneering a new approach with single-course gene editing medicines aimed at transforming the care of patients with or at risk for ASCVD. We are initially developing VERVE-101 for the treatment of HeFH, a genetic cardiovascular disorder that causes life-long elevated LDL-C levels and leads to early-onset ASCVD. We are initially developing VERVE-201 for the treatment of HoFH, a genetic cardiovascular disorder that causes extremely elevated LDL-C levels. If we successfully develop VERVE-101 for the treatment of patients with HeFH, we believe it could also be used to treat the broader population of patients with established ASCVD who are not at LDL-C goal on oral therapy. Ultimately, we believe these treatments could be potentially developed for administration to people at risk for ASCVD as a preventative measure. We are currently enrolling HeFH patients in our heart-1 clinical trial in New Zealand and the United Kingdom. We plan to report initial safety and pharmacodynamic data from the dose-escalation portion of the heart-1 clinical trial in the second half of 2023.
- *Expand our pipeline of gene editing treatments within ASCVD and beyond to additional CVD indications***.** We are expanding beyond our PCSK9 and ANGPTL3 programs with other early stage discovery programs, including one directed at Lp(a), another root cause of ASCVD, using a novel gene editor tailored to target the LPA gene. We intend to develop a suite of single-course gene editing medicines that comprehensively and robustly address additional independent causes of CVD. We believe our approach may be applicable to additional CVD indications with high unmet need driven by mutations in target genes expressed in the liver.
- *Expand portfolio of single-course in vivo gene editing programs through strategic relationships.* In July 2022, we established an exclusive, four-year global research collaboration with Vertex Pharmaceuticals Incorporated, or Vertex, focused on discovering and developing an *in vivo* gene editing program for a single undisclosed liver disease using a novel gene editor tailored to the gene target. We may enter into additional collaborations intended to develop novel *in vivo* gene editing programs for targets of interest.
- *Leverage our expertise and access to multiple gene editing technologies to become the leader in gene editing for CVD.* We believe that the deep expertise of our team in human genetics, gene editing and off-target analysis combined with multiple in-licensed technologies, including base editing and CRISPR nucleases, positions us to be able to develop single-course gene editing medicines designed to make a precise, predictable and permanent change in a target gene for the treatment of CVD. For each new target, our expertise allows us to systematically evaluate multiple gene editing technologies, including developing novel gene editing technologies, in primary human hepatocytes, mice and NHPs to identify the optimal approach based on potential efficacy and safety. We believe that our focus on developing gene editing medicines to treat CVD enables us to move rapidly and has culminated in the first ever patient dosed with an *in vivo* base editor.

We are also working to develop novel gene editors tailored to a particular target of interest, including as part of our Vertex collaboration and our research efforts for our Lp(a) program.

- *Advance LNP delivery technology leveraging both external as well as internal LNP capabilities to deliver gene editors to the liver*. On a target-by-target basis, we evaluate the best options for non-viral delivery from our external partnerships or our internal LNP discovery platform. For our lead program, VERVE-101, we have licensed LNP technology from Acuitas, an established company with a track record of partnering and developing LNPs for clinical use. We have also licensed lipid technology from Novartis which we intend to use in research and development of certain product candidates. Additionally, our internal team's expertise in biodegradable LNP chemistry, formulation and manufacturing has allowed us to develop and screen potent, liver-directed LNPs, including novel liver-targeting GalNAc-LNPs, which may offer superior delivery in certain CVD patient populations. We are utilizing proprietary GalNAc-LNPs in addition to the licensed Novartis lipid technology to deliver VERVE-201 to the liver. We are also evaluating GalNAc-LNPs to deliver a base editor targeting the PCSK9 gene.
- *Prioritize rapid iteration of product candidates in NHP preclinical models as an early development strategy*. We believe that studies in NHPs are a powerful predictor of efficacy in humans for gene editing and LNP delivery to the liver. Our preclinical validation approach prioritizes NHP experiments early in the process, enabling us to rapidly optimize drug product development to identify a lead candidate to take into clinical development. With VERVE-101 and VERVE-201, the bulk of our preclinical studies have been performed in NHPs, allowing us to establish the pharmacodynamic relationship between liver editing and resulting reductions in circulating PCSK9 protein, ANGPTL3 protein, and LDL-C that we believe will translate into humans.
- *Develop manufacturing capabilities to produce in vivo gene editing medicines at scale.* We are currently working with Good Manufacturing Practice, or GMP, vendors to produce all components of our drug candidates for our clinical trial batches. We have successfully executed batches at clinical scale through our vendors. We have also developed proprietary production processes designed to yield high-purity and high-quality mRNA that are crucial for *in vivo* liver editing applications. We are continuing to invest in building internal manufacturing capabilities for mRNA and LNP production, in order to fulfill our vision of delivering gene editing medicines to millions of patients with CVD.
- *Build the leading cardiovascular gene editing company by maintaining a dynamic culture that attracts and retains a talented and collaborative team.* We have attracted a talented team of scientists, cardiologists, drug developers and business professionals, as well as experts in the fields of human genetics, gene editing technologies, mRNA biology, off-target analysis and genetic medicine delivery modalities. Developing gene editing medicines that transform the care of CVD requires that we solve many new and complex problems as a natural component of the drug discovery and development process. Our vision, values, talent and strategy are essential to maximizing our ability to address these problems and bring forward a new approach to treating the leading cause of the death in the world.

Our approach

We are employing a tailored approach aimed at developing single-course gene editing medicines to transform treatment for patients with CVD. Our gene editing programs target validated genes in the liver that are supported by extensive human genetics and human pharmacology data and are known to be implicated in CVD. We use base editing, a next-generation gene editing approach that enables precise and efficient editing at the single base level in the genome without making a double-stranded break in the DNA, for our initial programs, including VERVE-101 and VERVE-201. Our gene editing programs consist of LNPs that encapsulate mRNA encoding for a gene or base editor as well as a gRNA targeting the gene of interest expressed in the liver. We believe that the following key elements of our approach will help us achieve our goal of delivering gene editing treatments on a global scale for millions of patients with CVD.

Editor selection

We selected gene editing as the core technology to develop our single-course gene editing treatments for CVD because we believe it offers the potential for durability of effect and versatility in the type of genetic modification compared to other genetic medicine approaches, including gene therapy and RNA therapeutics. We have access to multiple gene editing technologies through licenses including base editing and CRISPR nucleases. We are also seeking to discover new gene editing technologies. We believe having the flexibility to apply different gene editing technologies to different single-course treatments for CVD enables us to identify the best potential option for any given therapeutic application.

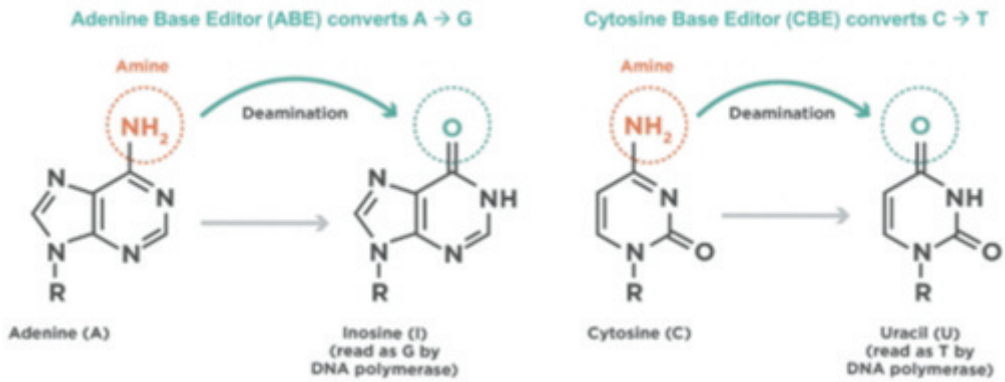
CRISPR-Cas Editing

CRISPR-Cas is a form of nuclease-based gene editing that enables targeting of genomic DNA sequences with high specificity in human cells by assessing for a match between the gRNA sequence and the DNA sequence. The gRNA allows the Cas protein to recognize a complementary part of the DNA sequence. Once RNA-DNA pairing occurs, the Cas enzyme makes a double-stranded DNA break, and the cell's natural DNA repair mechanisms work to make changes or repair the genome. When the repair is faulty, there can be disruption of a target gene, known as a knockout. CRISPR-Cas is effective at knocking out, or silencing, a targeted gene through disruption. However, potential limitations of standard CRISPR-Cas gene editing include lack of predictability in genetic outcomes and potential toxicities associated with double-stranded DNA breaks.

Base Editing

Base editing is a next-generation gene editing approach that enables precise and efficient editing at the single base level in the genome without making a double-stranded break in the DNA. If CRISPR-Cas gene editing approaches are akin to "scissors" for the genome, base editors are akin to "pencils," erasing and rewriting one letter in a gene.

Through our license agreement with Beam, we have access to two different types of base editors—adenine base editors, or ABEs, and cytosine base editors, or CBEs, each of which has a modified Cas9 protein bound to a gRNA, retaining the ability to target a genomic sequence, yet avoiding double-stranded DNA breaks. The base editors are distinguished by the kind of deaminase, the base editing enzyme that carries out the chemical modification, that is fused to Cas9. The deaminase makes a predictable chemical modification, called deamination, of the amine group on either an adenine, or A, base or a cytosine, or C, base as shown in the figure below.



For VERVE-101 and VERVE-201, we are using an ABE to convert an amine group of A to an inosine, or I, base, which is read by DNA polymerase as a guanine, or G, base, leading ultimately to an A-to-G spelling change. Once the initial modification has occurred, the intermediate DNA consists of an edited strand, containing an I at the target site, and an unedited strand with a thymine, or T, base. The I:T base pair is a mismatch, which the cell will normally attempt to repair in a process that can potentially lose the edit. In order to preserve the editing, our base editors cleave the unedited single strand of the DNA, referred to as nicking, rather than creating double-stranded breaks. The presence of the nick on the unedited strand, however, increases the efficiency of editing by inducing the cell to use the newly edited strand, and not the unedited strand, as the template for repair, resulting in an I:C base pair. Upon DNA repair or replication, the I is read as a G, resulting in a G:C base pair, and the permanent conversion of an A:T base pair to a G:C base pair is completed. This single base pair change at the specific site within the PCSK9 or ANGPTL3 gene alters the gene in such a way that no functional PCSK9 or ANGPTL3 protein is made, disrupting its role in maintaining elevated levels of circulating blood lipids.

Target selection

We focus on validated genes in the liver-cardiovascular axis, which are genes predominantly expressed in the liver and where disrupting protein production or introducing a beneficial mutation may effectively treat an underlying cause of CVD. When considering targets for our programs, we evaluate the following criteria:

- human genetic evidence that loss-of-function, or LoF, mutations confer resistance to disease;

- human genetic evidence that LoF mutations do not have adverse effects, and that homozygous LoF, inheriting two mutant alleles, are well tolerated;
- human clinical proof-of-concept data for targeting with other modalities to support the potential safety and efficacy of permanent gene or base editing;
- technical efficiencies, such as liver-predominant expression and known estimates of the pharmacodynamic relationship between target protein and therapeutic effect;
- existence of circulating protein biomarkers for efficacy, clinical biomarkers of disease modulation, and the availability of appropriate preclinical disease models; and
- clear unmet medical need and development rationale for the target indications.

Evaluating for off-target editing

Gene editing enables precise alterations at specific locations in the genome but has the potential to make alterations at undesired locations, known as off-target editing. Base editing has inherently fewer risks for off-target editing than CRISPR-Cas nuclease editing given the precision and efficiency of editing at the single base pair level and ability to make the edit without making a double-stranded DNA break.

Our approach to minimizing off-target editing involves the use of multiple orthogonal assays that provide a comprehensive assessment of the potential for off-target editing with our editors. These include in vitro methods that detect editing at single-nucleotide resolution via DNA sequencing, such as ONE-seq which utilizes a computationally designed synthetic DNA library with sequence similarity to the on-target locus or Digenome-seq where DNA extracted from cells provides an un-biased assessment of edited loci. Both methods provide a complementary and rigorous workflow for candidate site nomination. We have also developed a highly sensitive hybrid capture assay for assessing these nominated candidate sites and assays for assessing structural variants and guide-independent effects across the genome and transcriptome. We believe that our internal expertise in the application of multiple innovative techniques to evaluate off-target editing gives us a leading position in the field and the ability to rapidly advance future programs.

Lipid nanoparticle delivery selection

Gene editing treatments require intracellular delivery of mRNA and gRNA molecules into the target cell type—in our case, hepatocytes in the liver—and all of our programs utilize a non-viral approach, LNPs, for delivery. LNPs are well-established, both by approved products and by clinical trials conducted by others with other agents, to preferentially accumulate in the liver after systemic administration. We have chosen non-viral LNP delivery due to the potentially superior safety profile compared with available viral delivery approaches, as well as the high efficiencies of liver editing achievable with LNPs due to their natural tropism to the liver.

Non-viral delivery to the liver with LNPs confers potential advantages, including:

- protection of the mRNA and gRNA payloads while in circulation in the blood;
- transient expression of gene editing proteins, allowing more control over the editing process;
- transient expression of the editing protein and rapid completion of the editing process within days, minimizing immunogenicity;
- absence of DNA or viral components, avoiding exogenous DNA capable of inserting into the genome;
- rapid degradation of drug product within one to two weeks, supporting the potential for long-term safety;
- known, manageable infusion-related side effects; and
- cost-effective manufacturing with potential to efficiently scale to reach millions of patients.

To date, our LNP discovery platform has yielded novel proprietary ionizable lipids that we have designed, synthesized and evaluated for their potential to deliver gene editing payloads to the liver in mice. We are further optimizing and scaling up such formulations for evaluation in NHPs. We have also developed novel targeting ligands that when added to LNPs allow for more efficient delivery of RNA payloads to the liver.

On a target-by-target basis, we evaluate the optimal LNP delivery options from either external partnerships or our internal LNP discovery platform. For our lead program, VERVE-101, we have licensed LNP technology from Acuitas, an established company with a track record of partnering and developing LNPs for clinical use. Our collaboration with Acuitas included several NHP studies to evaluate various LNP formulations and RNA payloads prior to selecting an Acuitas LNP for VERVE-101. For VERVE-201, we have licensed LNP technology from Novartis and plan to use internally developed GalNAc-LNP technology for delivery.

We view our internal LNP discovery platform as an important source of delivery technology for future therapeutic programs. We are optimizing our internal LNP discovery platform by focusing on:

- strategies to enhance delivery to the liver in certain CVD patient populations, such as patients with HoFH, in whom LNP-mediated delivery may be challenging;
- improved efficiency of delivery to the liver, such that lower doses of RNA payload could be used;
- wider therapeutic indices to optimize the benefit-risk profile of our product candidates; and
- improved stability and potential for powder formulation enabling easier storage for commercial application.

We believe that our internal LNP discovery platform will yield improvement in our product candidates for current and future programs.

We are continuing to invest and build out capabilities in the development of novel and optimized GalNAc-targeting ligands, optimal lipid anchors, optimal compositions and ratios of LNP components, and optimal processes of addition and LNP formation with targeting ligands. We believe GalNAc provides a delivery platform for patients with both forms of FH and potentially may be applicable in other applications where liver-directed delivery is advantageous.

Single-course therapy

We are designing our single-course gene editing treatments to be administered as single-dose regimens through intravenous infusion, which is supported by data generated in our preclinical studies in NHPs. However, an advantage of using LNPs is the potential for split-dosing. In the case of our gene editing programs, we may elect to dose patients using a single, short course consisting of a limited number of split-doses over a short period of time to improve safety, efficacy or both. In patients who may not receive an adequate therapeutic effect with a single course of treatment, our approach may enable the option to re-dose. Patisiran, an approved LNP-encapsulated siRNA, is chronically administered without safety and efficacy concerns for patients with transthyretin amyloidosis, or ATTR. This is in contrast to viral vectors, which face safety and efficacy challenges with re-dosing.

The value of a single-course gene editing treatment will be determined by the safety, potency and durability of its desired effect. We believe a single-course treatment with VERVE-101 could durably lower LDL-C throughout the lifetime of patients with or at risk for ASCVD. Our gene editing treatments are designed to make a permanent change in the DNA of liver cells. With VERVE-101, transient expression of ABE protein in hepatocytes is designed to lead to permanent editing of the PCSK9 gene. Since liver cells turn over predominantly through division of hepatocytes that themselves will carry the PCSK9 edit, we believe that the efficacy resulting from the edit will be durable.

This stands in contrast to gene therapy, where the therapeutic benefit has been challenged by a lack of durability. Gene therapies are often designed to express exogenous mRNA by viral delivery or viral expression of mRNA. The durability of therapeutic effect can be limited by the loss of mRNA expression from a viral vector that does not integrate into the genome. This leads to either a reliance on viral integration at unpredictable sites in the genome, which can lead to safety challenges, or on repeat dosing that has its own challenges with viral delivery.

We believe that single-course gene editing treatments could provide durable and transformative outcomes, producing sustained health benefits for patients with CVD.

Scalable manufacturing

By designing our gene editing treatments as LNPs encapsulating mRNA and gRNA, we expect to benefit from the potential for scalable and cost-effective manufacturing processes enabling the opportunity to treat millions of patients with CVD.

Our product candidates are similar to two validated and approved drug classes: LNP-encapsulated siRNAs, such as patisiran, and LNP-encapsulated mRNA-based COVID-19 vaccines, which are LNPs containing a long mRNA molecule for the spike protein of SARS-CoV-2. Significant and ongoing investments are being made by multiple organizations to enhance the supply chain for all components and processes related to mRNA production, LNP production and fill-finish, especially in light of the intense worldwide efforts to manufacture massive quantities of COVID-19 vaccines. We believe we will ultimately benefit from the increased global capacity for LNP-encapsulated mRNA production over the next several years.

We are currently working with GMP vendors to produce all components of our drug candidates for our clinical trial batches. These include plasmid DNA preparation, mRNA production via in vitro transcription reactions, gRNA

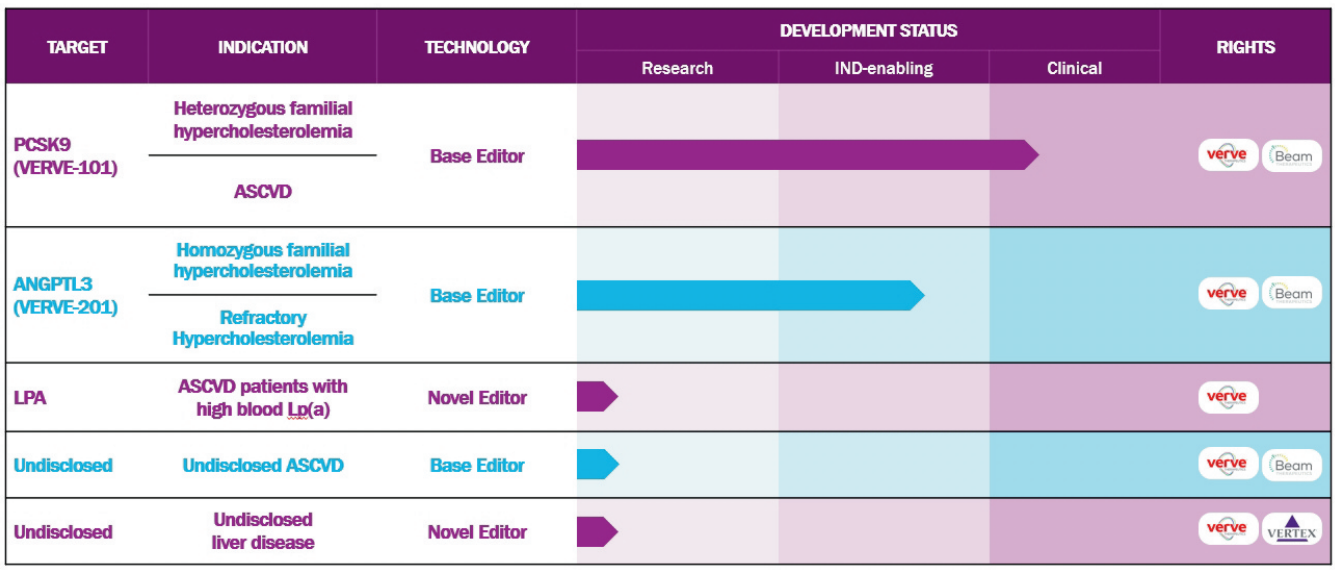
synthesis via solid state synthesis, lipid synthesis and LNP formulation and fill finish. Working closely with these vendors, we have successfully executed batches at clinical scale.

We are also investing in the buildout of internal process development capabilities in mRNA production and LNP formulation, which we believe will become one of our core competencies in the future. The goals of this internal process development capability are to scale up plasmid DNA, mRNA and LNP production batches, to make improvements in order to enhance quality, consistency and stability, and to reduce costs. Further, we are investing in analytical method development including bioactivity and potency assays that will be critical to further product development, batch comparability assessments and additional manufacturing growth.

Our gene editing programs

We are advancing a pipeline of single-course *in vivo* gene editing programs intended to durably turn off genes in the liver implicated in CVD. Our gene editing programs consist of LNPs that encapsulate mRNA encoding for a gene editor as well as a gRNA targeting the gene of interest expressed in the liver. Our pipeline is focused on genes implicated in the control of blood lipids, as well as other liver-mediated targets in and outside of CVD. We are developing our lead programs initially for the treatment of patients with forms of FH, which is a genetic disorder leading to life-long severely elevated blood LDL-C and increased risk of early-onset ASCVD. Patients with FH have mutations predominantly in the LDLR gene that affect the ability of liver cells to remove LDL from the circulation. FH manifests clinically in two forms: the more common heterozygous form, known as HeFH, and the rarer homozygous form, known as HoFH.

The following graphic summarizes our pipeline of programs.



Our most advanced product candidate, VERVE-101 targeting the PCSK9 gene, is currently being studied in heart-1, our Phase 1b clinical trial evaluating the safety and tolerability of VERVE-101 administration in a high risk subset of patients with HeFH in New Zealand and the United Kingdom. Genetically defined HeFH affects approximately 1.3 million people in the United States, 2.1 million in the European Union and the United Kingdom and approximately 31 million worldwide. We plan to report initial safety and pharmacodynamic data from the dose-escalation portion of the heart-1 clinical trial in the second half of 2023.

We are strategically developing VERVE-101 initially in patients with HeFH, recognizing that the unmet need is highest in those patients and the benefit-risk profile may be more favorable. We intend to use a stepwise clinical development plan for VERVE-101, evaluating efficacy and safety in higher-risk populations first, and then if successful, expanding into a broader population of patients with established ASCVD who are not at LDL-C goal on oral therapy, and ultimately to those at risk for ASCVD in the general population.

We plan to develop VERVE-201, our development candidate targeting the ANGPTL3 gene, using a similar stepwise approach. We plan to develop this program for the treatment of HoFH, which affects approximately 1,300 people in the United States, as well as people with ASCVD who are not at LDL-C goal on oral therapy and a PCSK9 inhibitor, or refractory hypercholesterolemia. Ultimately, we believe VERVE-201 may also be useful to people at risk for ASCVD as a preventative measure in the general population. We are conducting preclinical

studies to support a regulatory filing for the initiation of clinical development of VERVE-201 and anticipate initiating a Phase 1b clinical trial in 2024.

We intend to develop a broad pipeline of gene editing programs targeting distinct pathways implicated with ASCVD risk. Additionally, we believe our gene editing approach could have broader application for additional indications having both high unmet medical needs and validated gene targets expressed in the liver. With a focus on *in vivo* gene editing treatments, we plan to develop a suite of single-course gene editing medicines that address root causes of disease.

Familial hypercholesterolemia: our initial focus for our single-course gene editing treatments

FH is a genetic disorder where patients have life-long severely elevated blood LDL-C, which can lead to increased risk of early-onset ASCVD. FH is an autosomal dominant disease often caused by a mutation in the LDLR gene. Individuals with FH may harbor one mutant allele and are thereby heterozygous for the disease, known as HeFH, or two mutated alleles and are therefore homozygous for the disease, known as HoFH. HoFH is typically more severe than HeFH.

Men and women with untreated HeFH typically have LDL-C levels ranging from approximately 200 to 400 mg/dL and develop ASCVD before age 50 and 60, respectively. The estimated prevalence of genetically defined HeFH is roughly one in 250, which translates to about 1.3 million patients in the United States. Men and women with HoFH have LDL-C levels above 500 mg/dL and typically develop ASCVD before the age of 20 and, without intervention, die before age 30. The estimated prevalence of genetically defined HoFH is roughly one in 250,000, which translates to about 1,300 patients in the United States.

FH can be clinically diagnosed based on a combination of factors, including the concentration of blood LDL-C, physical findings, personal or family history of hypercholesterolemia and early onset of ASCVD. Extensor tendon xanthomas, typically Achilles, subpatellar and hand extensor tendons, with extremely elevated LDL-C levels are considered specific for FH. However, FH is often silent until the development of a heart attack at a young age, at which time a family history of ASCVD and elevated LDL-C levels are often the only findings. In an analysis of the FH phenotype, which typically means LDL-C levels of greater than 190 mg/dL, from six prospective cohort studies with 30-year follow-up, the FH phenotype was associated with up to a five-fold elevated 30-year ASCVD risk. ASCVD development was accelerated in those with the FH phenotype by 10 to 20 years in men and 20 to 30 years in women. In HoFH, patients typically develop atherosclerosis in childhood, initially in the aortic root, causing supravalvular aortic stenosis, and then extending into the coronary arteries. If the LDL-C level is not effectively reduced, people with HoFH die prematurely of ASCVD. The severity of atherosclerosis in FH is proportional to the extent and duration of elevated blood LDL-C levels.

Although the diagnosis of FH can be made on the basis of clinical features, genetic testing may offer additional insight into cardiac risk and diagnosis. Recent analysis of data from more than 26,000 individuals suggests that at any given LDL-C level, having an identified FH mutation is associated with significantly higher ASCVD risk than having the same LDL-C level but no apparent pathogenic FH mutation. In this analysis, individuals with an LDL-C level greater than or equal to 190 mg/dL and no pathogenic FH mutation had a six-fold higher risk of ASCVD than the reference group with an LDL-C level less than or equal to 130 mg/dL. However, individuals with an LDL-C level greater than or equal to 190 mg/dL and a pathogenic FH mutation were at a 22-fold higher risk of ASCVD than the reference group, possibly reflecting greater atherogenicity of life-long LDL-C elevation in FH compared with LDL-C elevation acquired later in life.

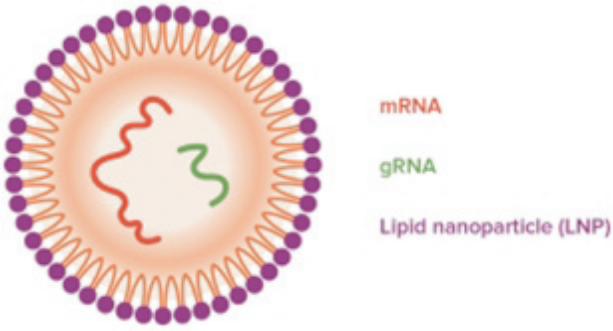
While dietary and lifestyle changes are important for LDL-C lowering in patients with FH, multidrug treatment is often required to achieve recommended LDL-C levels. The recommended LDL-C levels for FH patients are similar to those for non-FH patients with ASCVD. Treatment for FH patients tends to start earlier than those with or at risk for ASCVD without FH, and typically follows a more aggressive course with multidrug treatment given the elevated risk of early-onset ASCVD. While FH patients are treated with medicines similar to those used for non-FH patients, the chronic care for FH patients is typically more burdensome with earlier intervention and more drugs. In addition, for many patients, especially those with HoFH, their LDL-C levels remain inadequately controlled and do not reach goals recommended by clinical treatment guidelines.

VERVE-101: PCSK9 program

Our lead product candidate, VERVE-101, is designed to be a single-course *in vivo* gene editing treatment targeting the PCSK9 gene. We plan to develop VERVE-101 initially for patients with HeFH, and, if successful, to expand development for the broader population of patients who have established ASCVD and are not at LDL-C goal on oral therapy.

In patients with HeFH, a genetic mutation in the LDLR gene down-regulates LDLR expression, which limits the ability of liver cells to remove LDL from the bloodstream, resulting in extremely high LDL-C levels in the blood. Over time, high LDL-C builds up in the arteries, leading to formation of atherosclerotic plaque, reduced blood flow or blockage and ultimately heart attack or stroke. We believe that inactivation of the PCSK9 gene will result in lower PCSK9 protein levels, thereby increasing LDLR expression, leading to lower LDL-C levels and reduced risk for ASCVD. Clinical trials conducted by others evaluating PCSK9 inhibitors have suggested that targeting PCSK9 has the potential to work in patients with HeFH regardless of the underlying mutation.

VERVE-101 consists of an LNP encapsulating an mRNA encoding an ABE and a gRNA, as depicted in the image below. Four lipid components assemble along with the RNAs to form a dense, stable LNP that is approximately 60 nanometers in diameter.

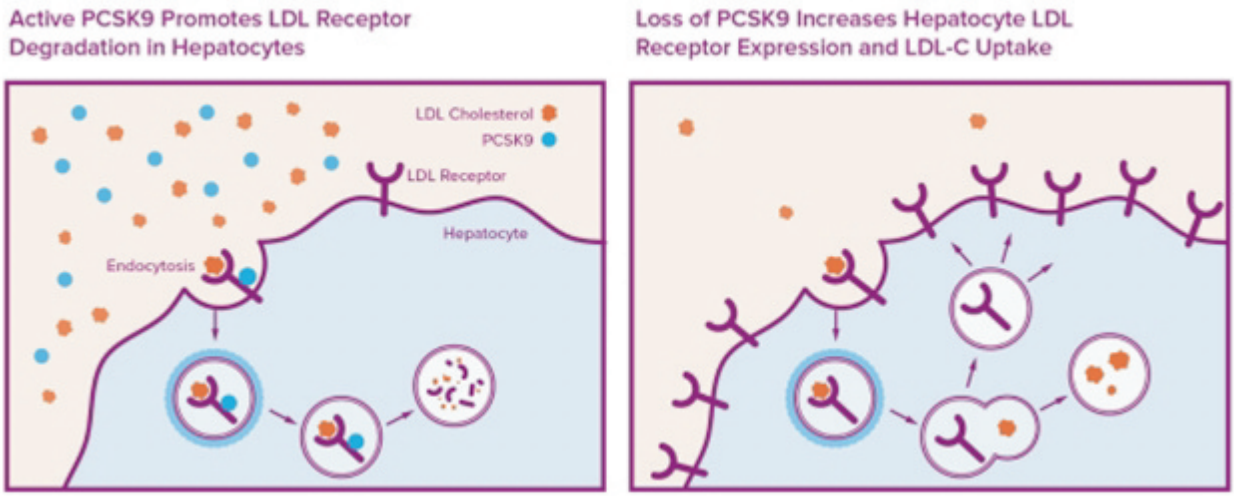


VERVE-101 is designed to be infused intravenously into the patient over approximately one to two hours, and then accumulates in the liver. Prior to administration of VERVE-101, a pre-medication regimen is given that consists of antihistamines and steroids. Once in the liver, VERVE-101 is brought into hepatocytes and escapes into the cytoplasm where the base editor protein is transiently expressed. The gRNA then binds to the base editor protein, and the complex is carried into the nucleus to locate the gene target specified by the 20-nucleotide spacer sequence of the gRNA. The ABE binds to the DNA and makes a single A-to-G spelling change at the target site, thereby turning off the PCSK9 gene. The ABE mRNA construct is codon-optimized and contains chemical modifications to reduce the potential for mRNA-mediated immune responses. The gRNA sequence has several chemical modifications to enhance *in vivo* stability to endonucleases and exonucleases.

PCSK9 as a target

The PCSK9 gene plays a critical role in the regulation of blood LDL-C through its regulation of the LDLR gene. The normal function of PCSK9 is depicted in the figure below on the left. The PCSK9 gene produces a protein in the liver that is released into the blood. LDLR is present on the surface of liver cells and binds to LDL and removes LDL from circulation. The LDL bound to LDLR is taken up by liver cells to enable the breakdown of LDL particles. LDLR is then recycled back to the surface of the cell, enabling the process of LDL uptake to recur. PCSK9 protein in the blood interrupts this LDLR recycling process. Specifically, PCSK9 protein in the blood binds to LDLR and targets LDLR for destruction. In doing so, PCSK9 reduces the number of LDLRs on the liver cell surface, thereby reducing the ability of the liver to clear LDL from the blood. The figure on the right depicts a loss

of PCSK9 gene function, which results in less PCSK9 protein and thereby increased LDLR expression and uptake of LDL-C.



As reported in *The New England Journal of Medicine*, one study found that adults with naturally occurring LoF mutations in the PCSK9 gene had LDL-C levels that were 38 mg/dL lower than adults without the mutation, and those with the mutation had an 88% lower risk of ASCVD. Human genetic studies also showed that carrying naturally occurring loss-of-function mutations in one or both copies of the PCSK9 gene was not associated with serious adverse health consequences.

In addition to human genetic studies, human pharmacology studies have provided validation for PCSK9 as a target. The impact of PCSK9 inhibition on cardiovascular outcomes has been established by two large, randomized, double-blind, placebo-controlled studies of two approved mAbs that bind to PCSK9 protein and block its activity, the FOURIER trial and the ODYSSEY OUTCOMES trial. The FOURIER trial demonstrated that treatment with evolocumab in addition to background statin therapy over a median of 2.2 years reduced major cardiovascular events by an additional 15% in patients with established ASCVD, with evidence of continued safety and increasing cardiovascular event reduction benefit that accrued over an additional 5.0 years of follow-up in the FOURIER open-label extension study. The ODYSSEY OUTCOMES trial demonstrated that treatment with alirocumab in addition to background statin therapy over a median of 2.8 years reduced major cardiovascular events by an additional 15% in patients with established ASCVD. Treatment with these mAbs demonstrated an approximately 60% reduction in LDL-C on average across clinical trials when compared with placebo treatment. Notably, in both trials, with the exception of injection site reactions, overall adverse event rates were similar between patients treated with placebo or drug, with no observed increase of new-onset diabetes, worsening glycemic control or neurocognitive adverse events.

The PCSK9 target has been further validated by inclisiran, which was approved by the EMA in 2020 and by the FDA in December 2021. In the ORION-9 trial, the pivotal Phase 3 trial of inclisiran in patients with HeFH, the percent change in the PCSK9 level after 510 days was a decrease of 60.7% in the inclisiran-treated group compared with baseline, which led to a reduction in LDL-C after 510 days of 39.7% compared to baseline.

We believe the human genetic studies and the human pharmacology with PCSK9 inhibitors provide substantial evidence that targeting PCSK9 is a potentially safe and effective approach to lower LDL-C and reduce ASCVD risk.

Preclinical studies

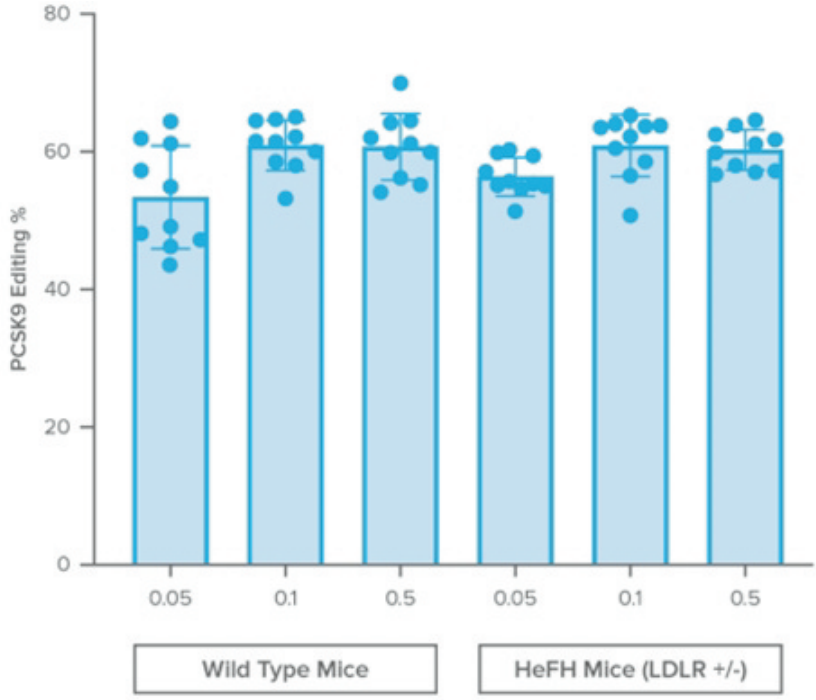
We discovered VERVE-101 based on extensive screening of a large library of gRNA candidates, evaluation of multiple LNP formulations and optimization of the ABE mRNA construct. We have tested a mouse surrogate of VERVE-101, precursor formulations of VERVE-101, which we refer to as our ABE-PCSK9 precursor formulation, and VERVE-101 itself *in vitro* and *in vivo* across multiple animal models. In these studies, we have observed the following:

- high PCSK9 gene editing activity in the liver by a mouse surrogate of VERVE-101 in both wild type mice and heterozygous LDLR knockout mice, a well-established mouse model of HeFH;

- two year NHP durability data for blood PCSK9 protein and LDL-C reduction following treatment with our ABE-PCSK9 precursor formulation, with average reductions of 90% of PCSK9 protein and 71% for LDL-C;
- dose-responsive liver PCSK9 gene editing, blood PCSK9 protein reduction, and LDL-C reduction in NHPs, with a 1 mg/kg dose of VERVE-101 achieving approximately 71% editing, approximately 85% reduction in blood PCSK9 protein and approximately 64% reduction in LDL-C;
- one year NHP durability data for blood PCSK9 protein and LDL-C reduction following treatment with VERVE-101, with average reductions of 89% of PCSK9 protein and 68% for LDL-C;
- VERVE-101 editing occurred predominantly in the liver and within 24 hours of treatment in NHP studies;
- evidence that VERVE-101 is potent in NHPs at doses as low as 0.5 mg/kg;
- no evidence of germline editing in an analysis conducted in sexually mature male NHPs receiving a 1.5 mg/kg dose of VERVE-101;
- no transmissions of the PCSK9 gene edit to the offspring of female mice treated with the murine surrogate of VERVE-101;
- sustained editing of the PCSK9 gene in regenerated liver lobes at 95 days post-treatment, as demonstrated in a partial hepatectomy mouse model designed to determine durability of PCSK9 base editing in the liver;
- administration of VERVE-101 to NHPs caused transient, mild elevations in liver function tests that entirely resolved within two weeks; and
- no significant off-target editing in primary human hepatocytes after evaluation at any of approximately 3,000 potential off-target sites.

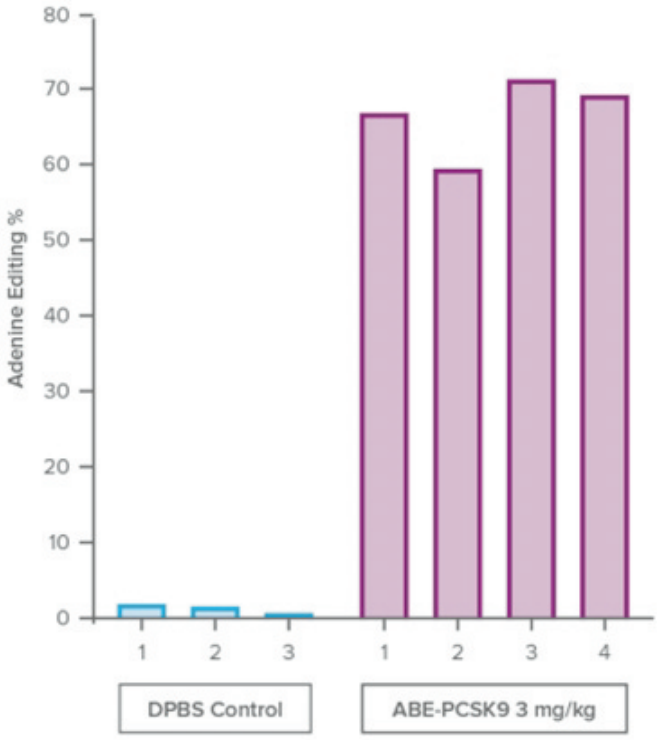
In vivo validation with ABE-PCSK9 mouse surrogate

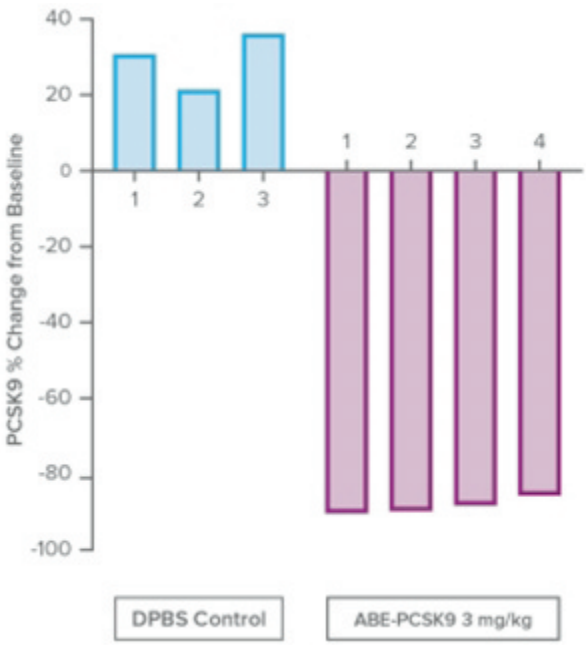
Our initial target patient population for VERVE-101 is patients with HeFH who produce reduced levels of functional LDLR, which results in increased levels of LDL-C in the blood. We utilized heterozygous LDLR knockout mice to model the HeFH disease state. A mouse surrogate version of VERVE-101 was developed for use in this model comprising a mouse surrogate gRNA targeting the ortholog of the same PCSK9 site, along with two components identical to VERVE-101—the ABE mRNA and LNP. As shown in the figure below, we observed that doses of 0.05, 0.1 and 0.5 mg/kg of the mouse surrogate of VERVE-101 administered once to wild-type and heterozygous LDLR knockout mice resulted in similar and robust amounts of PCSK9 editing in the liver.

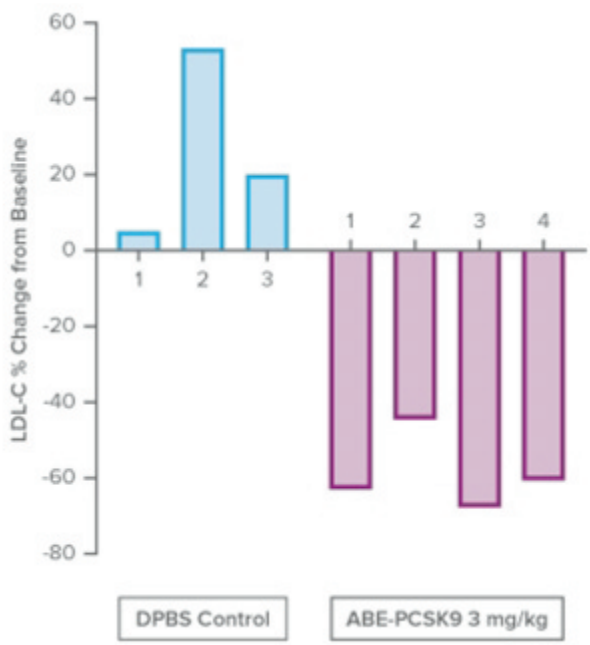


NHP validation with ABE-PCSK9 precursor formulation

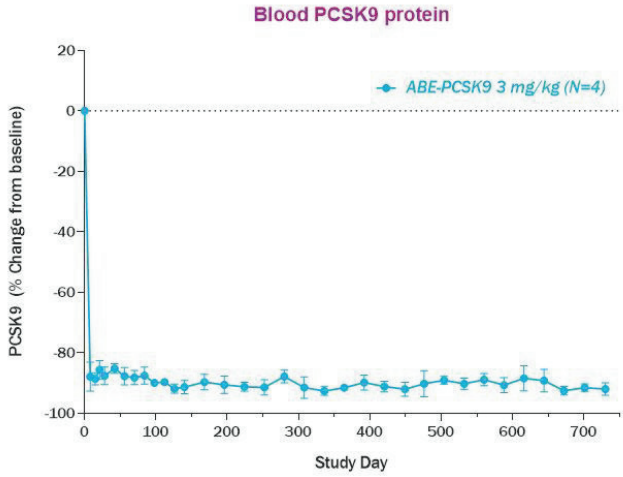
We then applied this approach in an NHP model to establish preclinical proof-of-concept using an ABE-PCSK9 precursor formulation. In this study, which is ongoing, we administered a single dose to healthy NHPs. In the figures below, each treated NHP is represented by a purple bar and each vehicle treated control is represented by a blue bar. Following a single treatment with our ABE-PCSK9 precursor formulation, we observed an average 67% editing of PCSK9 in whole liver tissue sampled through a liver biopsy two weeks after dosing, as shown in the first graph. This was accompanied by an average 89% reduction of blood PCSK9 protein and an average 59% reduction of blood LDL-C concentrations, as shown in the additional two graphs below.

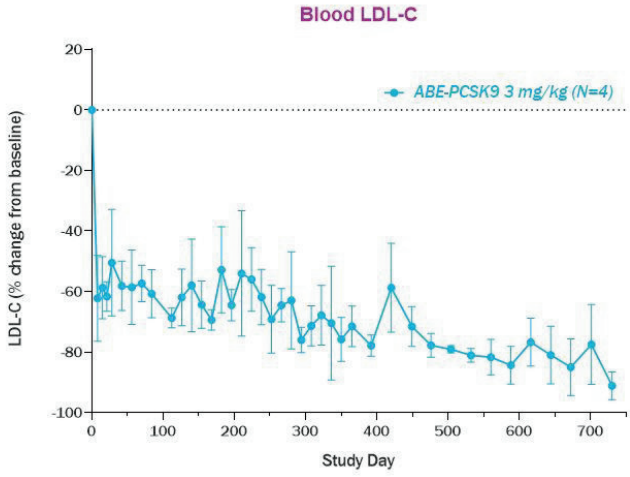






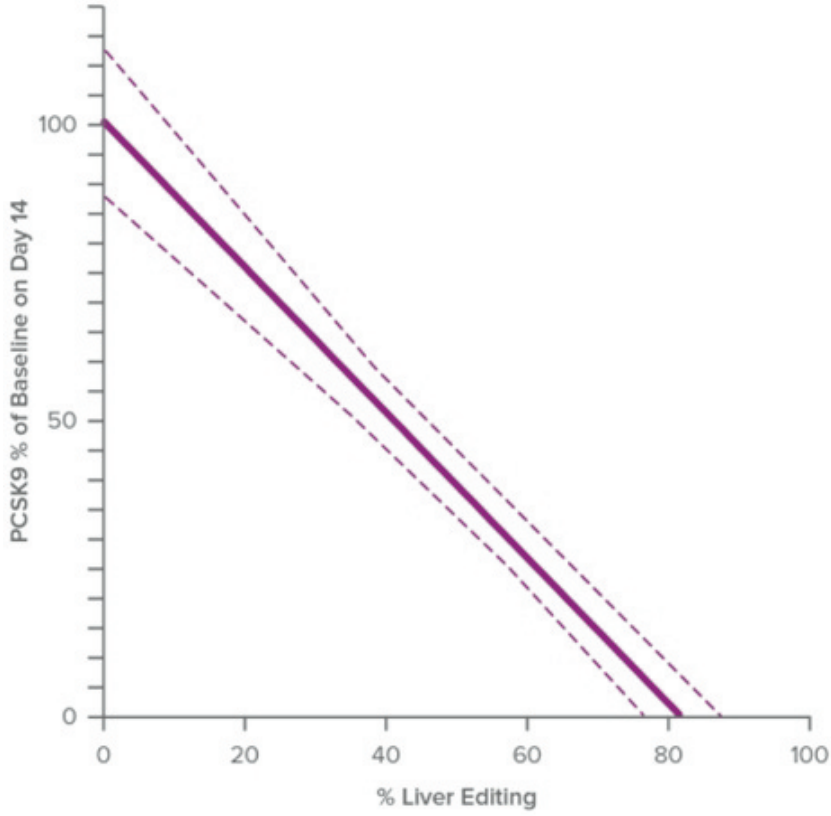
Importantly, in this preclinical study, we observed that the reductions in blood PCSK9 protein and blood LDL-C levels were durably maintained. As shown in the figures below, at two years following a single intravenous administration of ABE-PCSK9, we observed that the NHPs continued to exhibit an average 90% reduction in blood PCSK9 protein and an average 71% reduction in blood LDL-C.





Turnover of mature hepatocytes in the liver is estimated to occur on average every 200 to 300 days. The source of new hepatocytes is not certain, but evidence suggests that mature hepatocytes are responsible for production of new hepatocytes during both homeostatic liver turnover and following liver injury. Less likely, a fraction of hepatocytes with greater regenerative capacity may exist in the liver. In either case, the durability data shown above in our preclinical studies with an ABE-PCSK9 precursor formulation suggest that the liver cells responsible for regeneration are edited at the PCSK9 gene site. In addition, we have not observed evidence of persistent inflammation or liver injury that might suggest more rapid hepatocyte turnover or immune-mediated clearance of edited hepatocytes.

We have explored the pharmacodynamics of liver editing and consequent effect on blood PCSK9 protein levels across a large number of iterative NHP studies. We have identified a linear relationship between editing of the PCSK9 gene in liver cells and blood PCSK9 protein levels. The figure below shows a best-fit line with confidence intervals representing a large number of data points from individual NHPs. In NHPs, we have achieved a reduction of greater than 60% in PCSK9 protein with a whole liver editing rate of approximately 50% to 55%. We believe that this relationship between whole liver editing and PCSK9 reduction should be similar in humans.

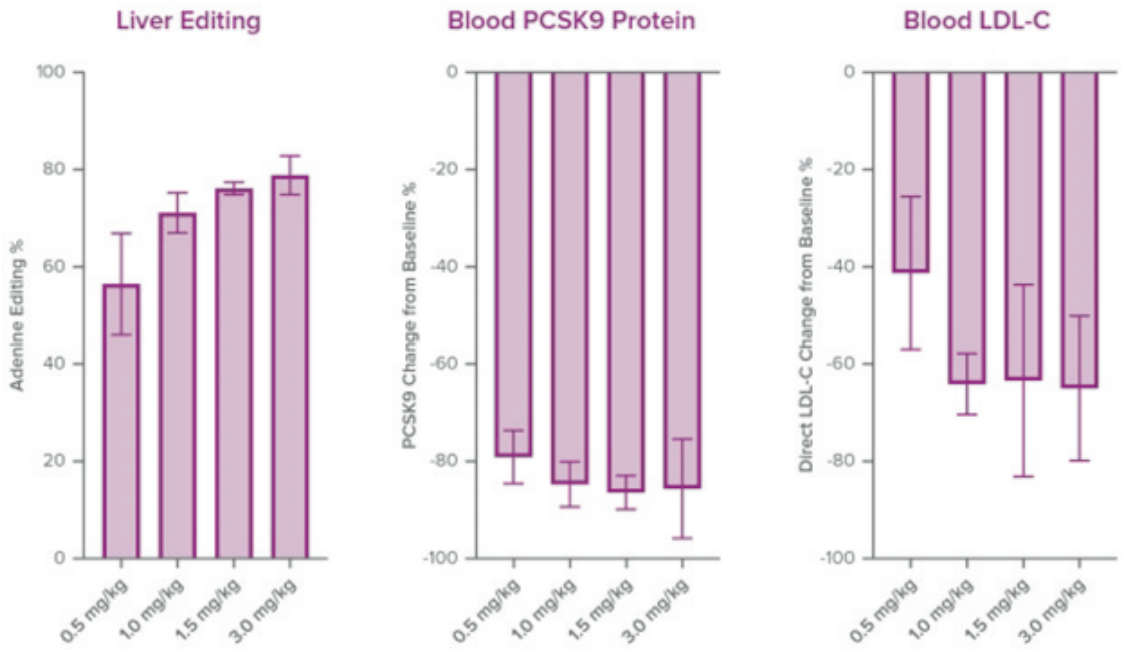


VERVE-101 preclinical efficacy data

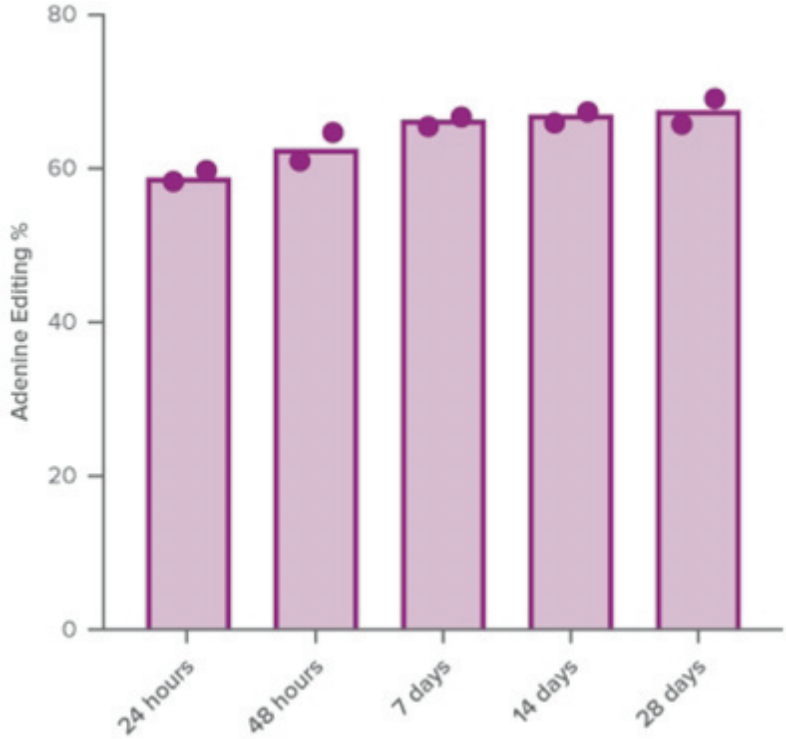
Our preclinical studies of our ABE-PCSK9 precursor formulation led to the development of VERVE-101.

Short-term preclinical study of VERVE-101

In a preclinical dose-response study of VERVE-101 in the figure below, in NHPs, we administered VERVE-101 at four dose levels with three NHPs per dose level. In the figure below each bar represents a different dose group ranging from 0.5 mg/ kg to 3.0 mg/kg. With a dose of 1 mg/kg, we observed whole liver editing levels of approximately 71%, as shown in the figure below, which we believe represents editing of the majority of hepatocytes. We also observed that the level of editing translated into dose-dependent reductions of both blood PCSK9 protein and blood LDL-C. At the 1 mg/kg dose, we observed a PCSK9 protein reduction of approximately 85% and a robust LDL-C reduction of approximately 64%.



We observed that editing occurred quickly following dosing of VERVE-101 in NHPs, with the majority of the editing observed within one to two days of dosing. In the study, NHPs (n=2 per group) were administered the same 1 mg/kg dose, and necropsies were serially performed on day one, day two, day seven, day 14 and day 28. We observed high efficiency editing within 24 hours with minimal additional editing at subsequent time points as shown in the figure below.



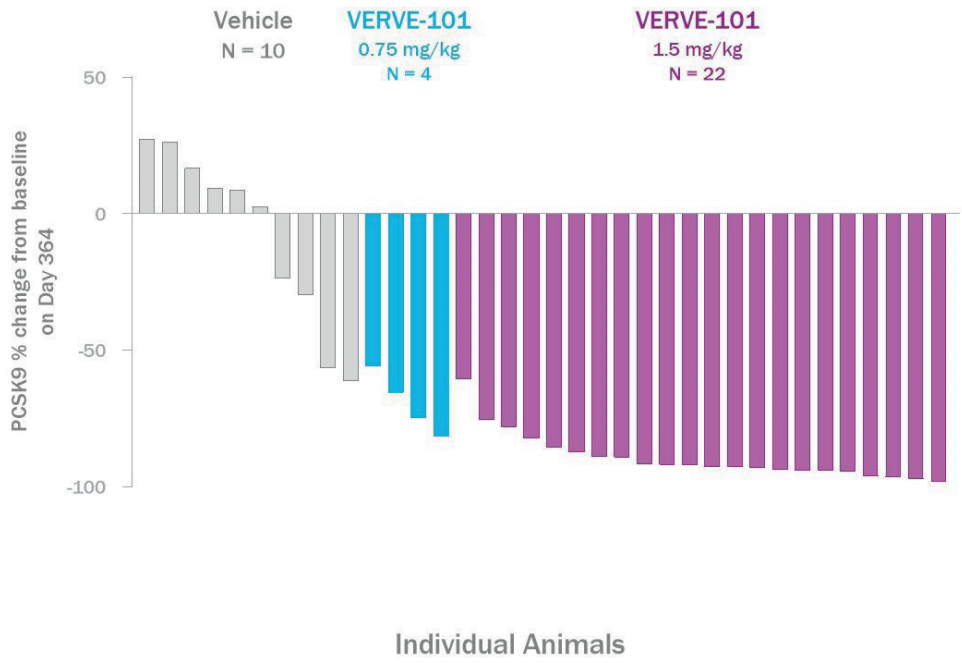
The effects on blood PCSK9 protein and LDL-C reached their peak outcomes within two weeks of dosing. The major component of the LNP, the ionizable lipid, is designed to be biodegradable and to be eliminated from the blood within two weeks, and we observed that it was largely eliminated from the liver, to less than 10% of peak concentration, within two weeks of dosing. ABE mRNA levels in the liver decreased by 97% within one week of dosing.

Long-term preclinical study of VERVE-101

In an ongoing long-term NHP study in 36 NHPs, we administered 1.5 mg/kg of VERVE-101 (n=22) and 0.75 mg/kg (n=4) with a control group (n=10). The study was designed to measure whole liver editing, blood PCSK9 protein levels and blood LDL-C levels. This study utilized our final VERVE-101 drug product that was manufactured at our planned clinical manufacturing site. We plan to continue this study in the dosed NHPs for three or more years.

With a dose of 1.5 mg/kg (n=22), we observed an average of 70% whole liver editing at the PCSK9 target site at day 15, as shown in the figure below, which we believe represents editing of the majority of hepatocytes.

At the 1.5 mg/kg dose, we observed a PCSK9 protein reduction of approximately 79% and a robust LDL-C reduction of approximately 62% at two weeks following treatment, which improved to 89% and 68% at one year following treatment. At a 0.75 mg/kg dose level (n=4), we observed a PCSK9 protein reduction of approximately 54% and a robust LDL-C reduction of approximately 38% at two weeks following treatment, which improved to 69% and 50%, respectively, at one year following treatment.

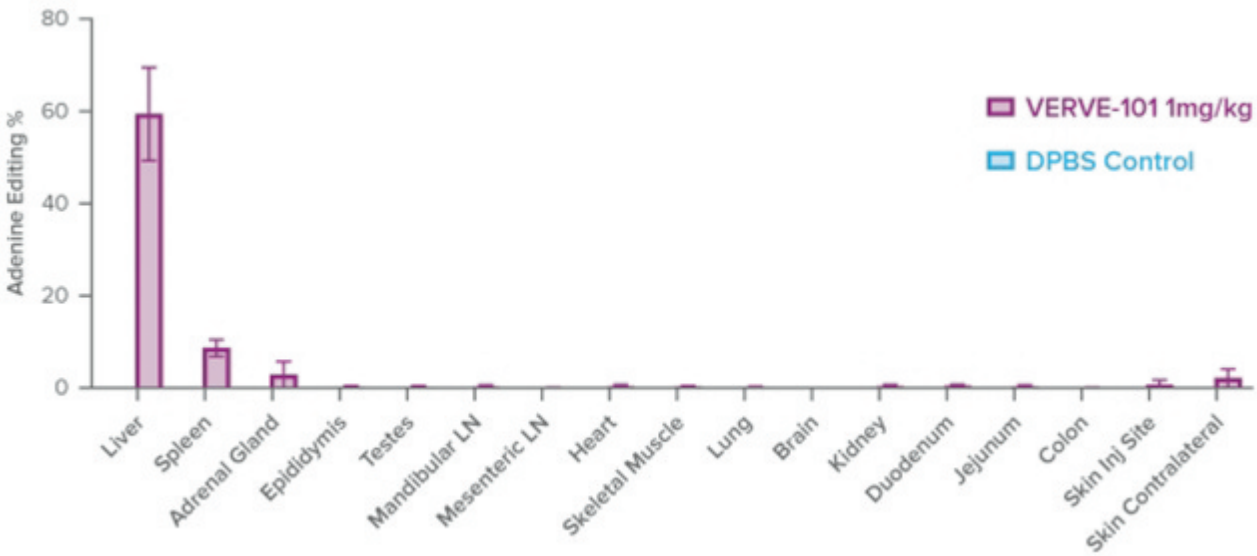


Partial hepatectomy mouse model

We conducted a durability challenge study in a partial hepatectomy mouse model in order to evaluate whether the level of editing remains following the turnover of liver cells. In this study, a partial hepatectomy that removed two-thirds of the liver or a sham surgery was conducted 11 days after dosing with a mouse surrogate of VERVE-101. In the mice with a partial hepatectomy, the rest of the liver regrows to restore liver weight in approximately nine days. We then performed a necropsy at either 22 days or 95 days post-treatment. We observed sustained editing of PCSK9 in regenerated liver lobes at both 22 days and 95 days post-treatment. We also observed sustained reductions in PCSK9 protein level at both 22 days and 95 days post-treatment. This data supports our belief that as the liver regenerates, the level of editing achieved by VERVE-101 is expected to remain robust and durable.

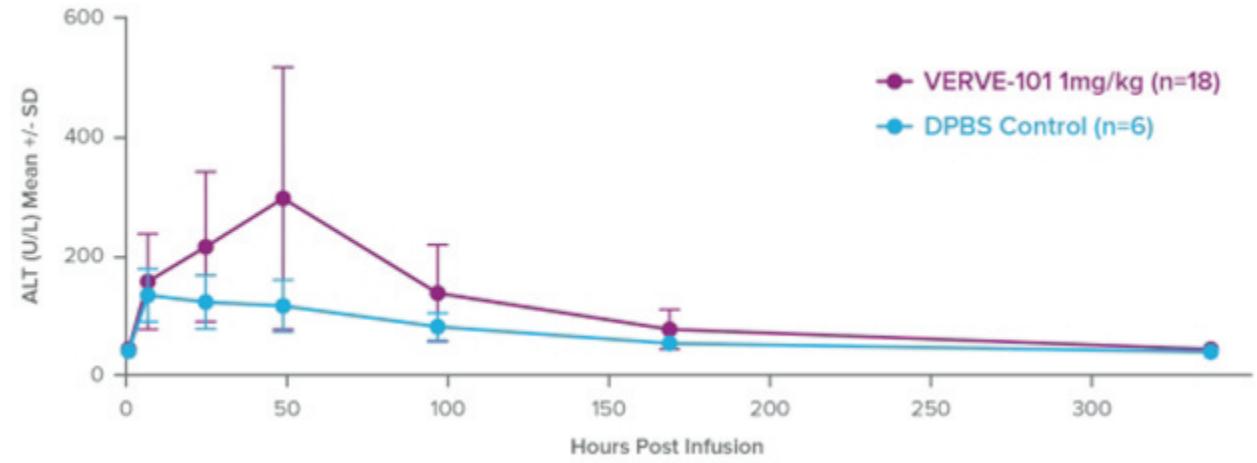
VERVE-101 biodistribution data

We are using an LNP-based approach to deliver VERVE-101 to the liver. An analysis of the biodistribution of VERVE-101 following administration of a single dose of 1 mg/kg in NHPs indicated that the large majority of editing occurred in the liver in a dose-dependent manner, with lesser rates of editing observed in the spleen and adrenal glands, as shown in the figure below. Other tissues examined showed editing of less than about 2%.



Tolerability of VERVE-101 in NHPs

VERVE-101 was generally well tolerated in NHP studies. We compared treatment with VERVE-101 to a control, or DPBS, at doses of 1 mg/kg or less and observed transient elevations of alanine aminotransferase, or ALT, consistent with mild acute liver injury within one to two days after dosing, which then peaked two to three days after dosing, with average values around 300 U/L following a 1 mg/kg dose. ALT is a commonly used blood marker of liver injury. Within one week of dosing, the average ALT value was within the normal range, indicating recovery, as shown in the figure below. These findings are consistent with observations from nonclinical studies performed for an approved LNP-based product that is administered intravenously.



The liver enzyme findings, which can be monitored with standard clinical laboratory testing, were consistently transient and mild in nature and fully normalized by one to two weeks. We believe that these findings compare favorably to viral vector delivery approaches, which can lead to unpredictable and acute liver injury.

In order to assess the long-term liver safety of VERVE-101, we monitored liver enzymes in a long-term durability study of an ABE-PCSK9 precursor formulation. We did not observe evidence of any ongoing inflammation in the livers of NHPs that had undergone high levels of PCSK9 editing in the liver. In contrast, viral vector delivery can have subacute and chronic liver injury as a result of autoimmune reactions to the viral vector.

In our ongoing long-term preclinical study of VERVE-101, we have not observed any long-term effects on liver function tests, and have only observed mild, transient increases in ALT levels, similar to the study described above. In this study, we also evaluated whether glucose homeostasis may be impacted by systemic PCSK9

inhibition. We have not observed any impact on glucose homeostasis up to one year following administration of VERVE-101.

In a study of 1.5 mg/kg dose of VERVE-101 in six sexually mature male NHPs, we did not observe evidence of germline editing at the PCSK9 site measured in a targeted amplicon assay at 11 weeks following treatment, which is greater than one full cycle of spermatogenesis.

In a study of 436 offspring of female mice treated with the murine surrogate of VERVE-101, genotyping of offspring showed that the PCSK9 gene edit was not transmitted to any of the offspring.

As LNPs are known to stimulate the immune system, we also assessed a panel of common cytokines following administration of a single dose of VERVE-101 in NHPs. At doses of 1 mg/kg or less, we observed mild and transient activation of certain cytokines, such as IP-10 or MCP-1, compared to control animals. This activation was apparent within 24 hours of dosing and fully resolved by the next observation point at one week. Other cytokines, including TNF-α, did not exhibit any changes above those seen in control animals.

We also assessed complement activation in NHPs that received single administration of VERVE-101. At doses of 1 mg/kg and less, we observed only minimal activation above that in control animals. This minimal activation was detectable approximately two hours after dosing but resolved by 24 hours.

Preclinical off-target editing in NHP

While the human genome is the relevant genome to assess off-target editing, we believe that evaluations of off-target editing in NHPs can support the ability of off-target analysis in primary hepatocytes *in vitro* to predict off-target editing in the liver when dosed *in vivo*.

Our approach to the identification of potential off-target sites includes a combination of bioinformatic and *in vitro* biochemical techniques, including ABE-Digenome-seq and a state-of-the-art technique called ONE-seq. ONE-seq is a comprehensive and sensitive *in vitro* method to screen for and identify potential sequences where editing may occur. Using ONE-seq, we evaluated the 25,000 sequences in the NHP genome most closely matching the sequence of our on-target site. We prioritized 45 potential sites where editing may occur, of which the PCSK9 target site was identified as the top site.

We then used next-generation DNA sequencing to assess these sites for editing in primary NHP hepatocytes treated with VERVE-101. As shown in the figure below, besides editing at the PCSK9 target site, we did not observe off-target editing at any of the 44 potential off-target sites evaluated, depicted by the purple dots, except for one site designated C5. The C5 site is not present in the human genome.

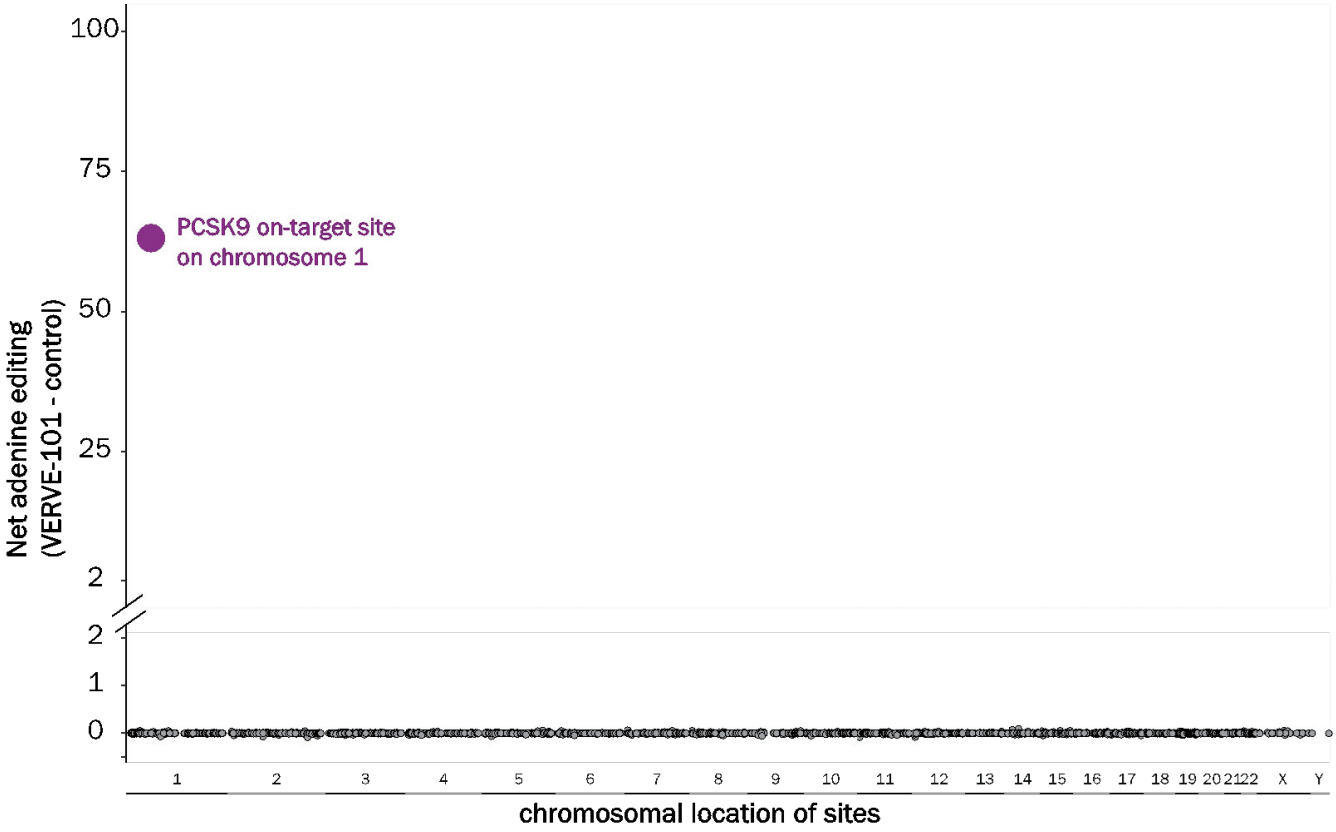
We then treated NHPs with VERVE-101, took NHP liver samples and sequenced the same sites that we evaluated in primary NHP hepatocytes. In NHP liver samples, we identified off-target editing only at the C5 site. These data support our belief that we have the ability to accurately predict off-target sites *in vivo* based on off-target analysis in primary hepatocytes *in vitro*.

Off-target analysis in primary human hepatocytes

Having established a methodology to connect off-target analysis in cells to *in vivo* editing, we turned to evaluation of the human genome for VERVE-101. Using two orthogonal techniques – the ONE-seq methodology and ABE-Digenome-seq—we prioritized more than 3,000 potential sites and assessed editing in primary human hepatocytes using a highly sensitive hybrid capture assay. As shown in the figure below, we did not observe any

significant net editing at any of the approximately 3,000 potential off-target sites (black circles) when compared to untreated cells and observed only on-target editing at the PCSK9 target site (purple dot).

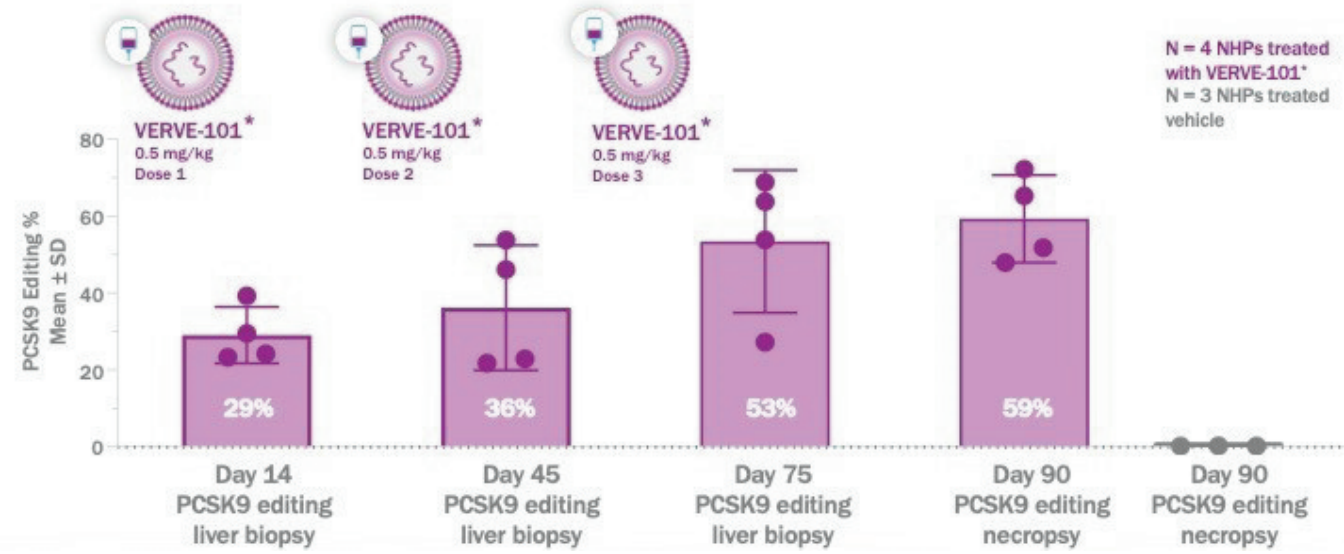
In April 2022, we presented data from a comprehensive preclinical assessment of the potential for VERVE-101 to cause unintended, or off-target, DNA edits in primary human liver cells from multiple donors. We used multiple methods consistent with recent guidance from the FDA to identify more than 3,000 sites with the greatest experimental or bioinformatic similarity to the on-target site. We then used a sequencing assay to determine whether administration of VERVE-101 resulted in off-target editing at those sites. We did not observe any statistically significant off-target editing after treatment with VERVE-101 at the identified sites. We also evaluated the potential for off-target editing in non-target cells (spleen cells, adrenal cells, and hematopoietic stem cells) and other cellular contexts (pediatric human liver cells and human liver cell lines) and identified only two sites with statistically significant editing above untreated controls. The two instances of off-target editing occurred at doses greater than the dose we expect to achieve saturation for on-target editing. Based on these assessments, we believe that VERVE-101 has a low risk of off-target genomic modifications that would be expected to have an associated clinical adverse effect.



In addition to the above analyses, we have evaluated for two other theoretical risks: editing of RNA by the base editor and translocations of DNA. In primary human hepatocytes, we did not observe any RNA editing above control or any translocations of DNA.

Preclinical study of multiple doses of VERVE-101

We are developing VERVE-101 as a single-course gene editing medicine. However, given the complexities of treating patients with ASCVD, we believe that some patients may benefit from additional lipid lowering after treatment with any single agent. We conducted a 90-day preclinical study of VERVE-101 in four NHPs to explore the potential to re-dose patients. In this study, we dosed 0.5 mg/kg of a VERVE-101 precursor on days 1, 30 and 60. We measured editing of PCSK9 by liver biopsy on days 14, 46 and 75, and by liver necropsy on day 90. As shown in the figure below, we observed an increase in PCSK9 editing over the course of the study, with an average of 29% at day 14, 36% at day 46, 53% at day 75 and 59% at day 90. We believe that these data suggest that repeat low doses of a PCSK9 base editor could achieve a high level of liver editing. We did not observe evidence of liver injury following any of the doses.



We believe these data highlight one of the potential key advantages of LNPs as a delivery approach for gene editing medicines.

Additionally, we have generated data indicating that our proprietary GalNac-LNP can efficiently deliver base editors targeting PCSK9, achieving approximately an 87% reduction in PCSK9 in wild-type NHPs. We are advancing a GalNAc-LNP delivered PCSK9 base editor into preclinical development and believe this data suggests that GalNAc-LNP delivery may have broad utility for liver editing in other indications.

heart-1 clinical trial

The heart-1 clinical trial is designed to enroll approximately 40 adult patients with HeFH who have established ASCVD and evaluate the safety and tolerability of VERVE-101 administration, with additional analyses for pharmacokinetics and reductions in blood PCSK9 protein and LDL-C. The trial includes three parts – (A) a single ascending dose portion, followed by (B) an expansion single-dose cohort, in which additional participants will receive the selected potentially therapeutic dose and (C) an optional second-dose cohort, in which eligible participants in lower dose cohorts in Part A have the option to receive a second treatment at the selected potentially therapeutic dose. During our interactions with regulators in New Zealand and the United Kingdom, country-specific protocols have been developed to account for various modifications to eligibility, design, and conduct in each country.

We have received clearance of our CTAs for VERVE-101 in New Zealand and the United Kingdom, and in July 2022, we announced that the first patient had been dosed with VERVE-101 in our heart-1 clinical trial. We have completed dosing of VERVE-101 in the first dose cohort of the dose-escalation portion of the heart-1 clinical trial. Enrollment efforts are ongoing in New Zealand and the United Kingdom. We plan to report initial safety and pharmacodynamic data for all dose cohorts of the dose-escalation portion of the heart-1 clinical trial in the second half of 2023.

VERVE-101 was recently awarded an Innovation Passport for the treatment of HeFH under the Innovative Licensing and Access Pathway, or ILAP, by the UK Medicines and Healthcare products Regulatory Agency, or the MHRA. The Innovation Passport designation is the entry point to the ILAP, which aims to accelerate time to market and facilitate patient access to medicines in the United Kingdom for life-threatening or seriously debilitating conditions, or conditions for which there is a significant patient or public health need.

We submitted our IND application to conduct a clinical trial evaluating VERVE-101 in patients with HeFH to the FDA in October 2022 and were subsequently informed by the FDA that our IND application was placed on hold. In December 2022, we received a clinical hold letter from the FDA that outlined the information required to resolve the hold, including additional preclinical data relating to: (i) potency differences between human and non-human cells, (ii) risks of germline editing, and (iii) off-target analyses on non-hepatocyte cell types. Clinical data from the ongoing heart-1 clinical trial in New Zealand and the U.K. were not included in the IND application package submitted to the FDA. In the clinical hold letter, the FDA requested available clinical data from the trial. In addition,

the FDA has requested that we modify the trial protocol in the United States to incorporate additional contraceptive measures and to increase the length of the staggering interval between dosing of participants. We intend to submit our response to the FDA as expeditiously as possible.

VERVE-201: ANGPTL3 program

VERVE-201, our development candidate targeting ANGPTL3, is designed to permanently turn off the ANGPTL3 gene in the liver. ANGPTL3 is a key regulator of cholesterol and triglyceride metabolism. We plan to develop this program for the treatment of HoFH, which affects approximately 1,300 people in the United States, as well as for refractory hypercholesterolemia defined as people with ASCVD who are not at LDL-C goal on oral therapy and a PCSK9 inhibitor. Ultimately, we believe that VERVE-201 may also be useful to people at risk for ASCVD as a preventative measure in the general population.

We are conducting preclinical studies to support a regulatory filing for the initiation of clinical development of VERVE-201 and anticipate initiating a Phase 1b clinical trial in 2024. We plan to utilize internally developed GalNAc-LNP technology in VERVE-201 to deliver a base editor targeting the ANGPTL3 gene to the liver. We have developed proprietary LNPs with a GalNAc ligand designed to bind to ASGPR in the liver, which bypass LDLR, thereby enabling uptake into the liver in HoFH patients.

ANGPTL3 as a target

The ANGPTL3 gene has recently emerged as a new and promising target for severe hyperlipidemia. The ANGPTL3 protein is produced almost exclusively in the liver and released into the blood. It was first identified as a regulator of cholesterol and triglyceride metabolism through genetic studies of a naturally occurring strain of mice with low cholesterol, low triglycerides and low circulating fatty acids. The main function of the ANGPTL3 protein is the inhibition of lipoprotein lipase, an enzyme on the surface of blood vessels in the heart, skeletal muscle and fat that is responsible for the breakdown and clearance of circulating triglycerides. ANGPTL3 protein has also been shown to regulate LDL-C by a mechanism that does not depend on LDLR expression, which is in contrast to the mechanism by which PCSK9 regulates LDL-C.

Human genetic studies, conducted by our founders, determined that naturally occurring loss-of-function mutations in the ANGPTL3 gene result in extremely low levels of triglycerides, LDL-C and high-density lipoprotein cholesterol. Subsequent studies determined that there were no apparent adverse health consequences observed in patients who naturally lack ANGPTL3 function. Furthermore, individuals completely lacking ANGPTL3 gene function were free from coronary atherosclerotic plaques evaluated by coronary computerized tomography, or CT, scan, compared to matched control family members. Two independent population genetic studies of individuals carrying a single mutated copy of ANGPTL3 demonstrated that partial loss of ANGPTL3 function is protective against ASCVD, with a 34% and 41% lower risk, respectively, compared to individuals without any ANGPTL3 mutations. Collectively, these studies provided strong evidence for ANGPTL3 as a potential therapeutic target for hyperlipidemia and ASCVD risk reduction.

Multiple therapeutic approaches targeting ANGPTL3 have been developed or are being evaluated in the clinic and provide further validation for ANGPTL3 as a target. Evinacumab is a mAb targeting ANGPTL3 that has been shown to effectively lower LDL-C and triglycerides in patients with HoFH and HeFH. The Phase 3 trial for evinacumab in patients with HoFH demonstrated a 49% reduction of LDL-C and a 50% reduction of triglycerides after 24 weeks compared to placebo. Based on these data, evinacumab was approved by the FDA in 2021 for the treatment of patients with HoFH.

The LDL-C lowering effect of evinacumab has been demonstrated to be additive to that of PCSK9 inhibition. In a late-stage clinical trial of patients with refractory hypercholesterolemia, due to HeFH in the majority of cases, the addition of evinacumab to a PCSK9 inhibitor further reduced LDL-C by 56% compared to placebo. In addition, other investigational agents targeting ANGPTL3 are being evaluated in patients with severe hypertriglyceridemia or CVD, including two different siRNA programs targeting ANGPTL3 from Arrowhead Pharmaceuticals (ARO-ANG3) as well as Eli Lilly.

Preclinical studies

In our early preclinical studies, we evaluated multiple LNP formulations with a view to enabling treatment of patients with all forms of FH, as well as multiple editor and gRNA options. In preclinical data generated to date, and discussed below, we have observed the following:

- development of a proprietary GalNAc-targeting ligand that when added to an LNP is capable of delivering a base editor to the liver independent of the LDL receptor status in mice, and which may potentially be used to treat patients with HeFH and HoFH;
- proof-of-concept data in NHPs for an ABE-ANGPTL3 precursor formulation demonstrating 60% whole liver editing, 95% reduction in ANGPTL3 and 64% reduction in triglycerides at two weeks after a single treatment;
- durability data in NHPs for an ABE-ANGPTL3 precursor formulation demonstrating an ANGPTL3 reduction of 97% and triglyceride reduction of 71% seen at two years following a single treatment; and
- proof-of-concept data in an internally developed NHP model of HoFH using a single treatment of two different formulations of our proprietary GalNAc-LNPs to deliver an ANGPTL3-targeted base editor demonstrating approximately 94% (n=3) and 97% (n=3) reduction in blood ANGPTL3 protein, respectively, and reductions in LDL-C of nearly 100 mg/dL, which was an approximately 35% reduction from baseline.

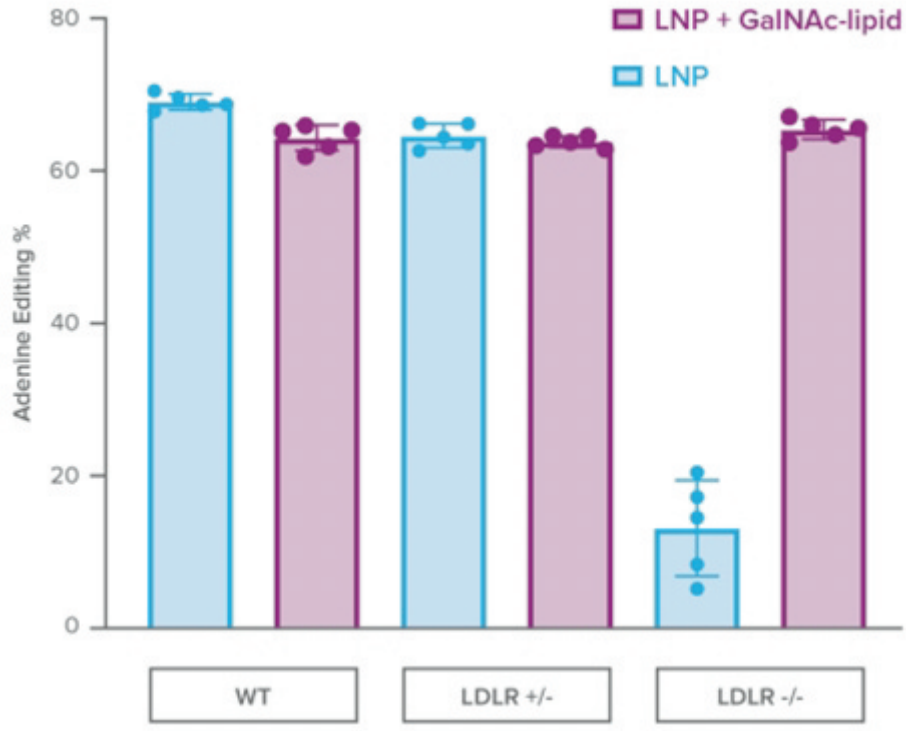
Discovery and validation of LNPs

Prior to nominating VERVE-201 as a development candidate, we used a rigorous process to optimize preclinical safety and efficacy. We performed a number of studies evaluating precursor formulations of an ANGPTL3 targeted base editor as well as multiple precursor formulations of our proprietary GalNAc-LNPs to deliver the editor.

LNP-mediated delivery to the liver is more challenging in patients with HoFH than in those with HeFH. This is due to the fact that deficiency in the LDLR gene often drives HoFH pathophysiology, and uptake of LNPs into the liver is generally thought to be through a predominantly LDLR-dependent pathway. An approach to bypass the LDLR would be the addition of a targeting ligand to LNPs that works through a receptor other than LDLR.

We have screened and developed a proprietary GalNAc-targeting ligand that can be incorporated into LNPs. GalNAc ligands bind to the ASGPR in the liver and have been used to enhance delivery of siRNAs to the liver. ASGPR is highly expressed in the liver with rapid turnover in about 15 minutes and high capacity to mediate uptake into the liver independent of LDLR.

We conducted a preclinical study in mice that were entirely deficient in the LDL receptor, or LDLR -/- mice, in order to evaluate the efficacy of our proprietary GalNAc-targeted LNPs. As shown in the graphic below, the addition of the GalNAc ligand onto the LNP increased editing in the liver of LDLR -/- mice. We observed that GalNAc-targeted LNPs have similar apparent potency in wild-type, LDLR +/- mice and LDLR -/- mice.



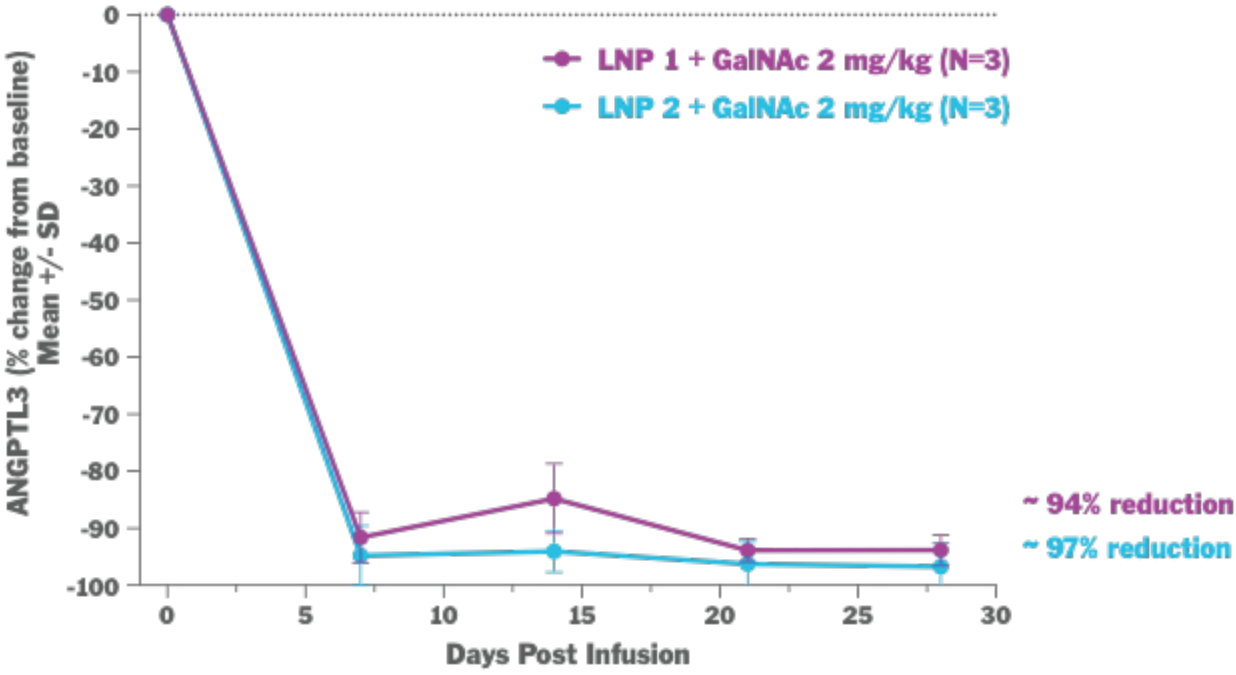
We are continuing to invest and build out capabilities in the development of novel and optimized GalNAc-targeting ligands, optimal lipid anchors, optimal compositions and ratios of LNP components, and optimal processes of addition and LNP formation with targeting ligands. We believe GalNAc provides a delivery platform for patients with both forms of FH and potentially may be applicable in other applications where liver-directed delivery is advantageous.

NHP model of HoFH

In order to create a model of HoFH in NHPs, we edited the LDLR gene in wild-type NHPs and eliminated LDLR expression in the liver using a Cas9 and dual guide RNA strategy encapsulated in standard LNPs, which led to nearly 70% whole liver DNA editing at the LDLR gene and resulted in an approximately 94% reduction in LDLR protein in the liver and a six-fold increase in blood LDL-C.

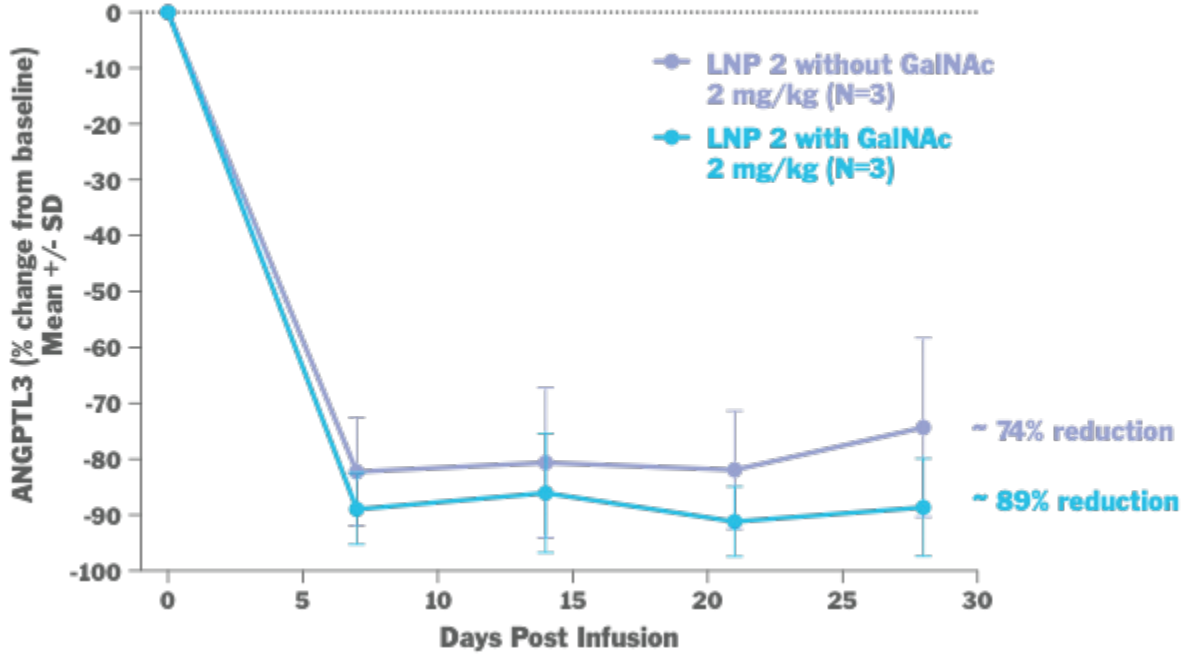
Validation in an NHP model of HoFH using internally developed GalNAc-LNPs

Using this novel NHP model of HoFH, we conducted a preclinical study using two different formulations of our proprietary GalNAc-LNPs to deliver an ANGPTL3-targeted base editor. In this study, we observed that delivery of the base editor using standard LNPs did not achieve effective ANGPTL3 editing in the liver of the NHP model of HoFH. As shown in the figures below, in NHPs treated with an ANGPTL3-targeted base editor delivered with a GalNAc-LNP, we observed approximately 94% (n=3) and 97% (n=3) reduction in blood ANGPTL3 protein, and reductions in LDL-C of nearly 100 mg/dL, which was an approximately 35% reduction from baseline.



GalNAc-LNP delivery to normal livers of NHPs

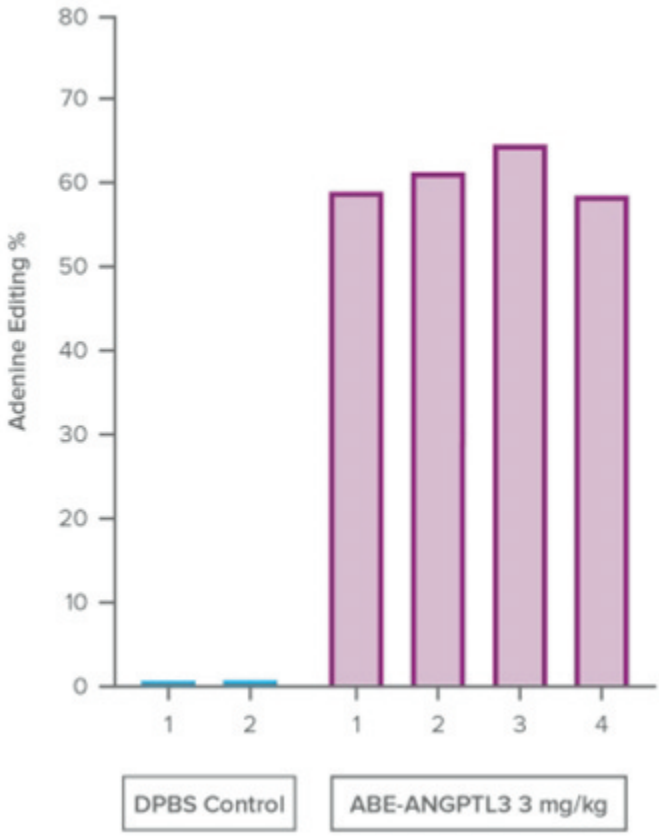
We have also assessed the potential broad utility of our proprietary GalNAc-LNP approach for delivery of an ANGPTL3-targeted base editor, in a preclinical study evaluating delivery efficiency of an ANGPTL3 base editor using both a GalNAc-LNP and a standard LNP without GalNAc in wild-type NHPs with normal livers. In these studies, we observed that wild-type NHPs treated with an ANGPTL3-targeted base editor delivered via our GalNAc-LNP had an approximately 89% reduction in ANGPTL3 protein compared to an approximately 74% reduction in wild-type NHPs treated with a standard LNP. We believe this suggests that GalNAc-LNP delivery may be utilized in indications where LDLR is present.



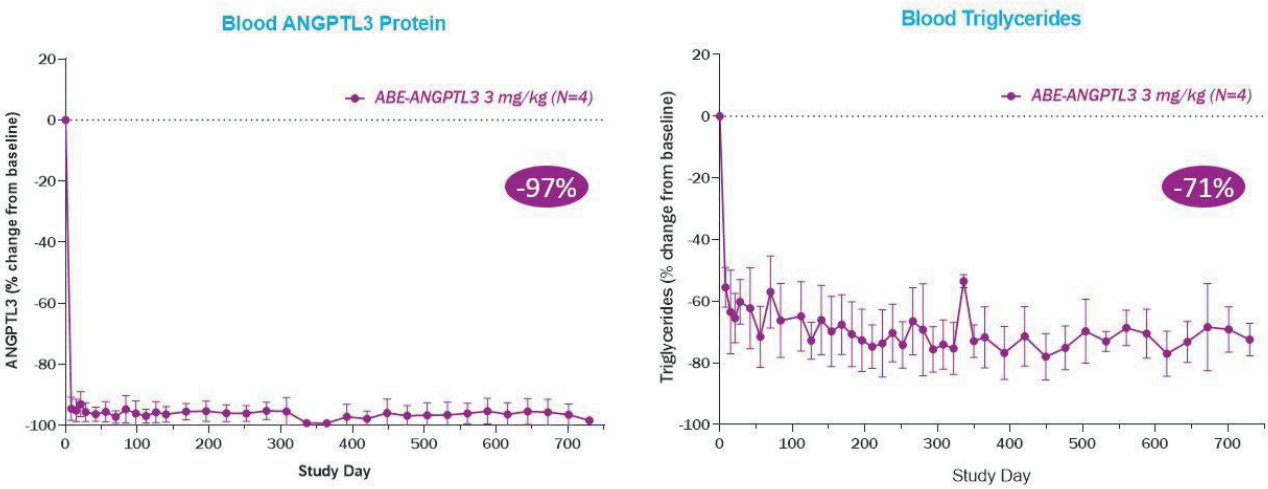
We have completed a large confirmatory dose-response study in 34 wild-type NHPs. In this study, we administered an ANGPTL3 base editor using a GalNAc-LNP at 1.5 mg/kg (n=6) and 3.0 mg/kg (n=16) with a control group (n=12). We observed a 96% reduction in circulating ANGPTL3 protein at the 3.0 mg/kg dose group.

NHP validation with ABE-ANGPTL3 precursor formulation

We conducted a preclinical proof-of-concept study using an ABE-ANGPTL3 precursor formulation. In this study, which is ongoing, we administered a single dose to healthy NHPs. In the figure below, each treated NHP is represented by a purple bar and each vehicle treated control is represented by a blue bar. Following a single treatment with our ABE-ANGPTL3 precursor formulation, we observed an average 60% editing of ANGPTL3 in whole liver tissue sampled through a liver biopsy two weeks after dosing. This was accompanied by an average 95% reduction of blood ANGPTL3 protein and an average 64% reduction of blood triglycerides concentrations.



Importantly, in this preclinical study, we observed that the reductions in blood ANGPTL3 protein and blood triglycerides levels were durably maintained. As shown in the figure below, at two years following a single intravenous administration of ABE-ANGPTL3, we observed that the NHPs continued to exhibit an average reduction of 97% in blood ANGPTL3 protein and an average reduction of 71% in blood triglycerides.



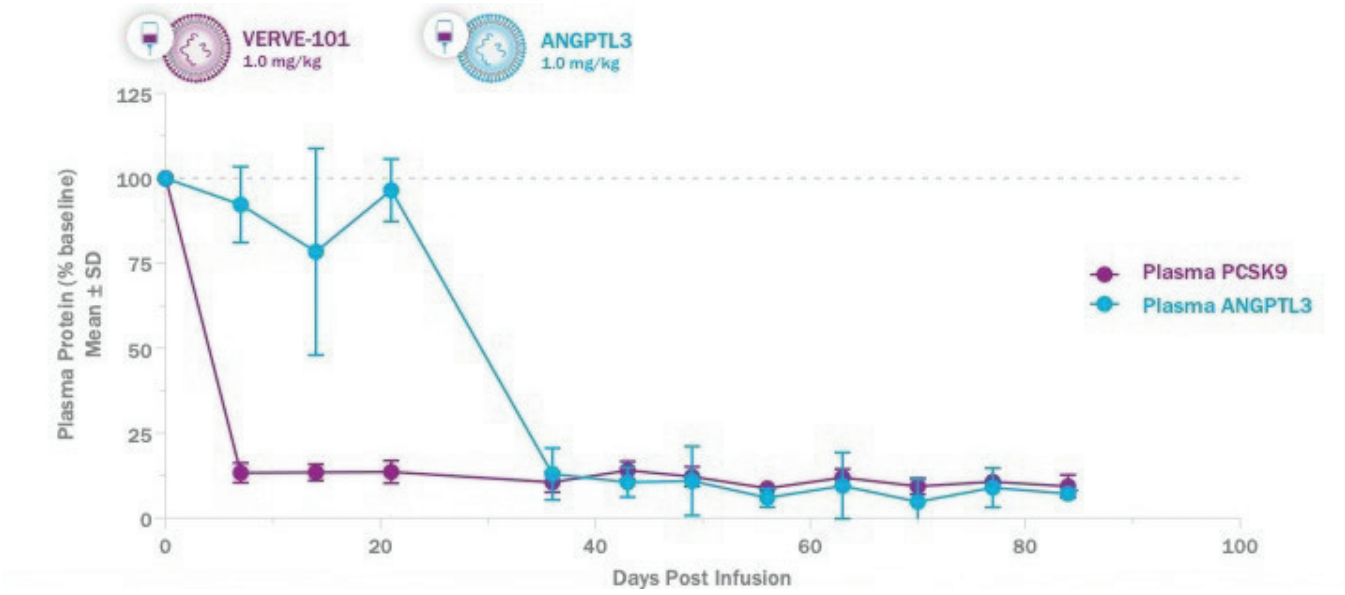
Our preclinical studies of our ABE-ANGPTL3 precursor formulation as well as precursor formulations of our proprietary GalNAc-LNPs led to the development of VERVE-201.

VERVE-201 next steps

Prior to nominating VERVE-201 as a development candidate, we used a rigorous process designed to optimize preclinical safety and efficacy. We selected an optimized configuration and evaluated VERVE-201 in primary human liver cells, which showed potent, on-target editing of the ANGPTL3 gene with no detectable off-target and no detectable structural variants as assessed using high-coverage whole genome optical mapping. We are conducting preclinical studies to support a regulatory filing for the initiation of clinical development of VERVE-201 and anticipate initiating a Phase 1b clinical trial in 2024.

Sequential dosing

We believe that patients with very high LDL-C levels or patients with hyperlipidemia that also have high LDL-C levels and high triglyceride levels may benefit from treatment with gene editing medicines that target two lipid pathways, such as PCSK9 and ANGPTL3. We conducted a 90-day preclinical study in four NHPs to assess the potential for sequential dosing of our base editors. In this study, we dosed 1.0 mg/kg of a VERVE-101 precursor on day 1, followed by a 1.0 mg/kg dose of an ANGPTL3 base editor on day 30. As shown in the figure below, we observed a substantial reduction of plasma protein levels of both PCSK9 and ANGPTL3 following sequential dosing. We measured PCSK9 editing by liver biopsy on day 15 and observed an average of 71% editing. We measured ANGPTL3 editing by liver biopsy on day 45 and observed an average of 52% editing. We conducted a liver necropsy on day 90 and observed an average of 69% PCSK9 editing and 63% ANGPTL3 editing. We also monitored plasma PCSK9 and ANGPTL3 protein levels during the study and observed a greater than 90% reduction of plasma PCSK9 protein after the first dose and a greater than 90% reduction of plasma ANGPTL3 protein after the second dose, and observed similar reductions at the end of the study. These data suggest that sequential dosing of a PCSK9 base editor followed by an ANGPTL3 base editor may be able to edit two genes that control two key lipid pathways.



Lp(a) Program

Our Lp(a) program is focused on designing an *in vivo* genome-editing medicine to durably inactivate the LPA gene in the liver with a precise DNA change. We plan to develop this program initially for patients with ASCVD and high circulating Lp(a) concentrations.

Lp(a) is a LDL-like particle with apolipoprotein B covalently linked to apolipoprotein(a) that is produced in the liver and circulates in the blood. The LPA gene target was prioritized based on epidemiologic, human genetic, and pharmacologic studies that have established Lp(a) as an important causal and modifiable driver of risk for ASCVD. This increased risk is most pronounced in individuals with very high Lp(a) concentrations (e.g., ≥ 150 nmol/L). An estimated 20% of ASCVD patients have a Lp(a) concentration above this threshold. Lp(a) concentrations are determined almost entirely by inheritance – lifestyle therapies and currently approved lipid-lowering therapies have minimal to no impact.

Both human genetics and pharmacologic studies have validated the potential efficacy and safety of a Lp(a)-reducing medicine. DNA variants that cause increased circulating Lp(a) are among the strongest inherited drivers of risk for ASCVD as well as certain heart valvular diseases (e.g., aortic stenosis). By contrast, naturally occurring loss-of-function mutations in one or both copies of the LPA gene are associated with protection from these conditions and no detectable serious adverse health consequences.

In addition to these human genetic studies, recent human pharmacologic studies of investigational therapies targeting LPA expression in the liver can potently lower circulating Lp(a) concentrations by greater than 80%. The potential for these medicines to lower the risk of recurrent ASCVD events in patients with high Lp(a) is being tested in ongoing cardiovascular outcomes trials of the antisense oligonucleotide pelecarsen and the siRNA olpasiran.

We believe that these prior studies – alongside our experience in developing *in vivo* genome editing medicines to treat ASCVD – provide substantial evidence for the potential utility of a single-course medicine to lower Lp(a) in a patient population with both high risk and high unmet need. Our Lp(a) program is in the early research stage.

Future opportunities

We are investing in the identification of additional *in vivo* liver gene editing treatments and intend to develop a suite of single-course gene editing medicines that address root causes of disease. We plan to continue to focus on programs where the target has biology substantially validated by human genetics and, in many cases, by clinical development programs using other modalities.

Manufacturing

We do not currently own or operate manufacturing facilities. We currently rely on third-party contract manufacturing organizations, or CMOs, and suppliers for critical starting materials, drug substances—gRNA, mRNA—and our drug products. We plan to use third-party CMOs to support our IND-enabling studies and to supply our clinical trials and commercial activities. As we scale manufacturing, we intend to continue to expand and strengthen our network of CMOs. We believe there are multiple sources for all of the materials required for the manufacture of our product candidates, as well as multiple CMOs who could assemble the components of our program candidates.

We are continuing to invest in building internal manufacturing capabilities for mRNA production and LNP formulation, including the development of novel and optimized GalNAc-targeting ligands, lipid anchors, optimal compositions and ratios of LNP components, and optimal processes of addition and LNP formation with targeting ligands. We are also investing in analytical method development including bioactivity and potency assays that will be critical to further product development, batch comparability assessments and additional manufacturing growth.

Manufacturing is subject to extensive regulations that impose procedural and documentation requirements. These regulations govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance. Our CMOs are required to comply with these regulations and are assessed by regular monitoring and formal audits. Our third-party manufacturers are required to manufacture any product candidates we develop under current Good Manufacturing Practice, or cGMP, requirements and other applicable laws and regulations.

We have personnel with extensive technical, manufacturing, analytical and quality experience to oversee our contracted manufacturing and testing activities.

Competition

The biotechnology and biopharmaceutical industries generally, and the CVD field specifically, are characterized by rapid evolution of technologies, sharp competition and strong defense of intellectual property. Any product candidates that we successfully develop and commercialize will have to compete with existing therapies and new therapies that may become available in the future. While we believe that our technology, development experience and scientific knowledge in CVD, gene editing and manufacturing provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions.

Many of the companies against which we are competing or against which we may compete in the future 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 and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of all of our product candidates that we develop for the treatment of CVD if approved, are likely to be efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than 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. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium to competitive generic products.

There are several approved products for LDL-C lowering or cardiovascular risk reduction, such as statins, ezetimibe, bempedoic acid, lomitapide, mipomersen and icosapent ethyl. There are several approved products that target PCSK9 protein as a mechanism to lower LDL-C and reduce the risk of ASCVD. Evolocumab, which is

a mAb marketed as Repatha by Amgen Inc., is approved by the FDA for the treatment of patients with HeFH, patients with HoFH and patients with ASCVD. Alirocumab, which is a mAb marketed as PRALUENT® by both Sanofi and Regeneron Pharmaceuticals, Inc., or Regeneron, is approved by the FDA for the treatment of patients with ASCVD and for the treatment of patients with primary hyperlipidemia, including HeFH. The approved mAb treatments act through extracellular inhibition of the PCSK9 protein. Inclisiran, which is a siRNA marketed as Leqvio® by Novartis, is approved in the United States for the treatment of patients with clinical ASCVD or HeFH who require additional lowering of LDL-C and in Europe for the treatment of patients with hypercholesterolemia, including HeFH, or mixed dyslipidemia. Inclisiran acts by inhibiting the synthesis of PCSK9 within liver cells, which is distinct from extracellular protein inhibition. We are also aware of three orally administered small molecule product candidates that target the PCSK9 protein as a mechanism to lower LDL-C and reduce the risk of ASCVD in various stages of clinical development. These include MK-0616 from Merck & Co., Inc, which was studied in a recently completed Phase 2b trial of adult patients with hypercholesterolemia with a plan to release results in the first quarter of 2023; an oral small molecule from Serometrix LLC in-licensed by Esperion Therapeutics, which disclosed plans in 2022 to submit an IND in late 2024 or early 2025; and AZD0780, acquired by AstraZeneca from Dogma Therapeutics, which is being evaluated in an ongoing Phase 1 clinical trial.

We are aware of two other gene editing programs targeting the PCSK9 gene in preclinical development. Precision Biosciences, Inc., or Precision, has published preclinical data showing long-term stable reduction of PCSK9 and LDL-C levels in NHPs following *in vivo* gene editing of the PCSK9 gene using its gene editing platform. In September 2021, Precision entered into a collaboration with iECURE under which iECURE plans to advance Precision's PCSK9 directed nuclease product candidate in to Phase 1 clinical trials for the treatment of FH in 2022. In January 2023, Precision announced that it had decided to cease pursuit of this program with iECURE as a partner, with plans to provide additional guidance on whether and when this medicine will advance into clinical testing in the future. Additionally, in 2022, CRISPR Therapeutics, or CRISPR, announced CTX330, its research stage *in vivo* gene editing program targeting PCSK9.

Evinacumab, which is a mAb targeting ANGPTL3 protein that is marketed by Regeneron, is approved by the FDA for the treatment of patients with HoFH and has additionally been evaluated in Phase 2 studies of patients with refractory hypercholesterolemia and either ASCVD or HeFH, and severe hypertriglyceridemia. We are aware of several product candidates in clinical development that target ANGPTL3 as a mechanism to lower LDL-C and reduce the risk of ASCVD, including ARO-ANG3, a siRNA targeting ANGPTL3 being evaluated by Arrowhead Pharmaceuticals in Phase 2 clinical trials of patients with HoFH and patients with mixed dyslipidemia. In 2022, Arrowhead announced plans to initiate pivotal Phase 3 studies of ARO-ANG3 in patients with HoFH and patients with HeFH in the second half of 2023. In addition, Eli Lilly and Company is evaluating a siRNA targeting ANGPTL3 protein in a Phase 2 study in adults with mixed dyslipidemia, and in 2022, CRISPR announced CTX310, its gene editing program targeting ANGPTL3, which is in IND-enabling studies with plans for initial patient dosing in 2023.

Several investigational medicines designed to reduce Lp(a) are currently in development. These include pelecarsen, an antisense oligonucleotide licensed by Novartis from Ionis Pharmaceuticals in 2019, which is being evaluated in the Phase 3 Lp(a) HORIZON cardiovascular outcomes study in patients with high Lp(a) and cardiovascular disease, with topline results expected in 2025. Olpasiran is an investigational siRNA medicine targeting Lp(a) licensed by Amgen from Arrowhead Pharmaceuticals, which was recently shown to lower Lp(a) concentrations in patients with established ASCVD and high Lp(a) concentrations. The potential for olpasiran to reduce cardiovascular events in patients with existing ASCVD and high Lp(a) will be evaluated in the OCEAN(a) study, which was initiated in 2022 with plans for study completion in 2026. In addition, SLN360 is an investigational siRNA medicine being developed by Silence Therapeutics plc that is being evaluated in an ongoing Phase 2 study of patients with high Lp(a) concentrations and high risk for ASCVD events, and, in 2022, CRISPR announced CTX320, its research stage *in vivo* gene editing program targeting Lp(a).

Intellectual Property

We strive to protect the proprietary technologies that we believe are important to our business, including pursuing and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technologies and other inventions that are important to our business. In addition to patent protection, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, including certain aspects of our technology.

Our commercial success depends in part upon our ability to obtain and maintain patent and other proprietary protection for commercially important technologies, inventions and know how related to our business, defend and

enforce our intellectual property rights, in particular, our patent rights, preserve the confidentiality of our trade secrets and operate without infringing valid and enforceable intellectual property rights of others.

The patent positions for biotechnology and pharmaceutical companies like ours are generally uncertain and can involve complex legal, scientific and factual issues. In addition, the coverage claimed in a patent application can be significantly reduced before a patent is issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our product candidates will be protected or remain protectable by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

As of December 31, 2022, our patent estate covers various aspects of our programs and technology, including our gene editing programs for PCSK9 and ANGPTL3 targets as well as our RNA delivery and other platform technology. Any U.S. or foreign patents issued or pending would be scheduled to expire on various dates from 2041 through 2043, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees. Further details on certain segments of our patent portfolio are included below.

PCSK9 program

With regard to our VERVE-101 program, as of December 31, 2022, our patent estate includes one pending U.S. patent application and over fifteen foreign application counterparts that we own or control and cover various aspects of our VERVE-101 program, including guide RNA sequences targeting the PCSK9 gene, mRNAs encoding adenine base editors, and compositions thereof, methods of using such compositions for therapeutic indications, methods for *in vivo* gene editing, formulations, dosing regimens, and combination therapies.

ANGPTL3 program

With regard to our VERVE-201 program, as of December 31, 2022, our patent estate includes one pending U.S. patent application, one pending international PCT application and over fifteen foreign application counterparts that we own or control and cover various aspects of our VERVE-201 program, including guide RNA sequences targeting the ANGPTL3 gene, mRNAs encoding adenine base editors, and compositions thereof, methods of using such compositions for therapeutic indications, methods for *in vivo* gene editing, formulations, dosing regimens, and combination therapies.

License and collaboration agreements

We are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. The licensed intellectual property covers, in part, CRISPR-related compositions of matter and their use for base editing. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future.

Collaboration and license agreement with Beam Therapeutics

In April 2019, we entered into a collaboration and license agreement with Beam, or the Original Beam Agreement, pursuant to which we received an exclusive, worldwide, sublicensable license under certain of Beam's base editing technology, as well as gene editing and delivery technologies to develop, make, use, offer for sale, sell and import base editing products and nuclease products using Beam's CRISPR associated protein 12b, or Cas12b technology, in each case, directed to any of four gene targets, including the PCSK9 and ANGPTL3 genes, that are associated with an increased risk of coronary diseases, or the licensed products. Upon execution of the Original Beam Agreement and as partial consideration for the rights granted to us thereunder, we issued 276,075 shares of our common stock to Beam.

In July 2022, we amended and restated the Original Beam Agreement upon entering into the Amended and Restated Collaboration and License Agreement with Beam, or the Amended Beam Agreement. Pursuant to the Amended Beam Agreement, Beam granted us an exclusive, worldwide, sublicensable license under certain of Beam's base editing technology to develop and commercialize products directed towards a third liver-mediated, cardiovascular disease target, in addition to the PCSK9 and ANGPTL3 gene targets licensed under the Original Beam Agreement. We are responsible for the development and commercialization of products targeting the licensed gene targets, in each case subject to Beam's opt-in right. Except as described below, we are fully responsible for the development of licensed products under the Amended Beam Agreement.

For the ANGPTL3 and PCSK9 gene targets, following the dosing of the final patient in a Phase 1 clinical trial of a licensed product for such gene targets, Beam has the right to opt-in to share 33% of worldwide expenses of the development of such licensed product, as well as jointly commercialize and share profits and expenses of commercializing such licensed products in the United States on a 50/50 basis. For the third gene target, following the dosing of the final patient in a Phase 1 clinical trial of a licensed product for such additional gene target, Beam has the right to opt-in to share 35% of worldwide expenses of the development of such licensed product, as well as jointly commercialize and share 35% of the profits and expenses of commercializing such licensed product worldwide.

If Beam exercises its opt-in right for a given licensed product, which we refer to following such opt-in as a collaboration product, it will be obligated to pay for a specified percentage of the development and commercialization costs of such collaboration product and will have the right to receive a specified percentage of the profits from any sales of such collaboration product. With respect to each collaboration product, we and Beam will enter into a subsequent co-promotion agreement prior to the anticipated sale of such collaboration product in the United States, pursuant to which we and Beam will each provide 50% of the promotional effort required to promote the collaboration product. For collaboration products, on a product-by-product basis outside of the United States, we are obligated to pay clinical and regulatory milestones of up to an aggregate of $5.6 million and sales-based milestones of up to an aggregate of $7.5 million.

We refer to any licensed products for which Beam has either (i) not elected to exercise its opt-in right or (ii) if Beam has exercised its opt-in right, either we or Beam subsequently elect to opt-out of the payment of shared development and commercialization costs and participating in the commercialization of such licensed product, as a non-collaboration product. For such non-collaboration products, on a product-by-product basis worldwide, we are obligated to pay clinical and regulatory milestones of up to an aggregate of $11.3 million and sales-based milestones of up to an aggregate of $15.0 million.

To the extent there are sales of a collaboration product outside of the United States or a non-collaboration product worldwide, we will be required to pay tiered royalties to Beam at rates ranging from the low-to-mid single digit percentage of net sales, subject to specified reductions. Such royalty payments will terminate on a country-by-country and product-by-product basis upon the later to occur of (i) the expiration of the last to expire valid claim under the patent rights covering such product in such country, (ii) the period of regulatory exclusivity associated with such product in such country or (iii) 10 years after the first commercial sale of such product in such country.

We granted to Beam an exclusive, worldwide, sublicensable, fully paid-up license under our intellectual property, including under our GalNAc-LNP delivery technology, relating to a preclinical program developed by us. Beam has a non-exclusive license under know-how and patents controlled by us, and an interest in joint collaboration technology, to allow Beam to conduct activities under agreed upon research and development plans, as applicable.

We and Beam each have the right to sublicense our licensed rights, subject to certain restrictions and provided that the sublicense agreement is in compliance and consistent with the terms of the Amended Beam Agreement and any applicable licensed agreements.

The Amended Beam Agreement granted Beam, on a target-by-target basis, the option to obtain a non-exclusive, worldwide, sublicensable license to our GalNAc-LNP delivery technology for the development and commercialization of certain base editor products, as to which Beam would owe us a fee upon exercise of each option, certain regulatory and commercial sale milestones as well as low single-digit royalties on net sales for base editor products using the GalNAc-LNP delivery technology.

Under the Amended Beam Agreement, Beam controls the prosecution of its respective patent rights, at its sole expense. We have the first right, but not the obligation, to file for, and prosecute and enforce, at our sole expense, product-specific patent rights under the Amended Beam Agreement, to the extent permitted by Beam's applicable in-license agreements, and we have the exclusive right to file for, prosecute and maintain the patent rights under our delivery technology and any other patent rights that we licensed to Beam under the Amended Beam Agreement.

With respect to intellectual property rights jointly developed by Beam and Verve arising out of a party's performance of its obligations under the agreement, such intellectual property, depending on its nature, is considered under the agreement as joint collaboration technology and subject to joint ownership by Beam and Verve and we and Beam shall decide in good faith as to who shall bear responsibility for filing for, prosecuting and maintaining the jointly owned patent rights.

The term of the Amended Beam Agreement continues until the last to expire of any royalty term for any licensed product. We have the right to terminate the Amended Beam Agreement as to any licensed product, but not for any collaboration product, by delivering a 90-day termination notice to Beam, provided that Beam has elected not to exercise its opt-in right or the period to exercise such opt-in right has expired. Beam has the right to terminate the Amended Beam Agreement as to certain products by delivering a 90-day termination notice to us. The Amended Beam Agreement may be terminated by either party upon (i) written notice if the other party is in material breach and fails to cure such breach within the specified cure period or (ii) the other party's bankruptcy or liquidation. Beam may terminate the Amended Beam Agreement, and we may terminate the licenses granted to Beam under the Amended Beam Agreement, immediately if the other party, directly or indirectly, challenges the enforceability, validity or scope of any patent rights underlying the licenses granted under the Amended Beam Agreement.

Acuitas agreements

License agreement for the PCSK9 gene target

In October 2020, we selected an LNP optimized under a development and option agreement with Acuitas, or the Acuitas Development Agreement, to be a component of our VERVE-101 product candidate. In connection with that selection, we exercised an option with respect to the use of the LNP technology and entered into a non-exclusive, worldwide license with Acuitas, or the Acuitas License Agreement, with a right to sub-license through multiple tiers, under the licensed LNP technology to research, develop, have developed, make, have made, keep, use and have used, sell, offer for sale, have sold, import and have imported, export and have exported and otherwise commercialize and exploit licensed products using the LNP technology in connection with the PCSK9 gene target for all human therapeutic or prophylactic uses. Under the Acuitas License Agreement, we are obligated to use diligent efforts to develop and commercialize licensed products.

Acuitas retained the right to prosecute and maintain, at its sole expense, patents related to the LNP technology. In the event that Acuitas elects not to file, prosecute or maintain patents related to the LNP technology, it will notify us and we have the right, but not the obligation, to request that Acuitas continue to file, prosecute or maintain such patents, at our expense, and our license to such patents will automatically become irrevocable, perpetual, fully paid-up and royalty free, but such patents will thereafter no longer be part of the licensed technology in such country.

We and Acuitas will enter into a joint patent prosecution and maintenance agreement with respect to the jointly owned patents under the Acuitas License Agreement and as further provided in the Acuitas Development Agreement.

We paid Acuitas an upfront license fee of $2.0 million (less previously paid target reservation fees) and are required to pay an annual license maintenance fee of $0.8 million until the achievement of a certain development-based milestone. We are also obligated to reimburse Acuitas quarterly for employee and reasonable external expenses incurred that are related to the transfer of its licensed technology to our CMO.

We are also obligated to pay Acuitas up to an aggregate of $9.8 million in clinical and regulatory milestones and $9.5 million in sales-based milestones. We will be required to pay royalties at a low single digit percentage based on annual net sales of licensed products sold by us, our affiliates or our sublicensees. Such royalty payments are subject to reduction if we obtain a license from a third party under technology relating to the LNP technology. Any such royalty payments are payable, on a country-by-country and licensed product-by-licensed product basis, until the later of (i) the expiration of the last to expire valid claim in the licensed technology that covers the licensed product in such country, (ii) the expiration of the regulatory exclusivity period in such country and (iii) ten years from the first commercial sale of the licensed product in such country.

The Acuitas License Agreement will terminate on a licensed product-by-licensed product and country-by-country basis upon the last-to-expire royalty term in such country with respect to such licensed product. We may terminate the Acuitas License Agreement without cause upon prior written notice to Acuitas. Either party may terminate the Acuitas License Agreement upon (i) written notice if the other party is in material breach and fails to cure such breach within the specified cure period or (ii) immediately upon notice in the event of the other party's bankruptcy or insolvency. In lieu of terminating the agreement for Acuitas' uncured material breach, we have the alternative option, upon written notice to Acuitas, not to terminate the agreement but instead reduce the applicable milestone and royalty payments by a specified percentage.

Novartis license agreement

In October 2021, we entered into a license agreement with Novartis to obtain a non-exclusive license to lipid technology that we are using in connection with the research and development of certain product candidates, including VERVE-201. As consideration for the license and rights granted under the agreement, we made a one-time, non-refundable, upfront payment of $0.8 million during the year ended December 31, 2021. The license agreement requires us to pay up to an aggregate of $10.0 million in clinical and regulatory milestones and $35.0 million in sales-based milestones for products that incorporate the licensed lipid technology.

In June 2022, we amended the agreement to include three additional licensed products to the scope of the non-exclusive license. In consideration of the additional licensed products, we were required to make a one-time, non-refundable upfront payment of $2.8 million to Novartis.

Cas9 license agreement with The Broad Institute and the President and Fellows of Harvard College

In March 2019, we entered into a license agreement with Broad and Harvard for specified patent rights and in December 2019, we entered into an amendment to this license agreement, or, as amended, the Cas9 License Agreement. The licenses granted to us under the Cas9 License Agreement include rights to (i) certain patents and patent applications solely owned by Harvard, or the Harvard Cas9-I Patent Rights, certain patents and patent applications co-owned by the Massachusetts Institute of Technology, or MIT, and Broad, certain patents and patent applications co-owned by The Rockefeller University, or Rockefeller, and Broad, and certain patents and patent applications co-owned by MIT, Broad and Harvard, which patents and patent applications licensed under the Cas9 License Agreement we refer to as the Harvard/Broad Cas9-I Patent Rights and (ii) certain patents and patent applications co-owned by MIT, Broad, Harvard and the University of Iowa Research Foundation, or Iowa, which patents and patent applications licensed under the Cas9 License Agreement we refer to as the Harvard/Broad Cas9-II Patent Rights, and together with the Harvard/Broad Cas9-I Patent Rights, the Harvard/Broad Cas9 Patent Rights.

In February 2017, Broad and Rockefeller entered into an inter-institutional agreement pursuant to which Rockefeller authorized Broad to act as its sole and exclusive agent for the purposes of licensing Rockefeller's rights in such Harvard/Broad Cas9-I Patent Rights.

In December 2014, as amended in August 2016, MIT, Iowa and Broad entered into a joint invention administration agreement pursuant to which Iowa authorized Broad to act as their sole and exclusive agent for the purposes of licensing their rights in such Harvard/Broad Cas9-II Patent Rights.

License rights under Cas9 License Agreement

Pursuant to the Cas9 License Agreement, Broad and Harvard granted us a worldwide, royalty-bearing, sublicensable license to the Harvard/Broad Cas9 Patent Rights to make, have made, use, have used, sell, offer for sale, have sold, import and export products directed to PCSK9, ANGPTL3 and two additional targets, in the field of the prevention and treatment of human disease, subject to certain limitations and retained rights. With respect to the Harvard/Broad Cas9-I Patent Rights and certain of the Harvard/Broad Cas9-II Patent Rights, or the Cas 9-II Group A Patent Rights, the license is co-exclusive with Editas Medicine, Inc., or Editas. With respect to certain other of the Harvard/Broad Cas9-II Patent Rights, or the Cas9-II Group B Patent Rights, the license is non-exclusive. The license follows the inclusive innovation strategy developed by Broad, MIT and Harvard.

Broad and Harvard also granted us a non-exclusive, worldwide, royalty-bearing, sublicensable license to the Harvard/Broad Cas9 Patent Rights for internal research purposes; for research, development and commercialization of products for the prevention or treatment of human disease outside the field of Editas' exclusive license agreements with Broad and Harvard; and with respect to the targets, to make, have made, use, have used, sell, offer for sale, have sold, import and export products that are not Cas9 licensed products but is a Cas9 enabled products.

The licenses granted by Broad and Harvard to us under the Cas9 License Agreement are subject to retained rights of the U.S. government in the Harvard/Broad Cas9 Patent Rights and the rights retained by Broad, Harvard, MIT, Rockefeller and Iowa on behalf of themselves and other academic, government and non-profit entities, to practice the Harvard/Broad Cas9 Patent Rights, as applicable, for research, educational or teaching purposes. In addition, certain rights granted to us under the Cas9 License Agreement for the Harvard/Broad Cas9-I Patent Rights are further subject to a non-exclusive license to the Howard Hughes Medical Institute for research purposes. Our co-exclusive license rights also are subject to rights retained by Broad, Harvard, MIT, Rockefeller and Iowa, for each of them and for any third party (including non-profit and for-profit entities), to research, develop, make, have made, use, offer for sale, sell, have sold, import or otherwise exploit the Harvard/Broad Cas9 Patent Rights and licensed products as research products or research tools, or for research purposes.

We have the right to sublicense our licensed rights, subject to certain restrictions and provided that the sublicense agreement must be in compliance and consistent with the terms of the Cas9 License Agreement. Any sublicense agreement cannot include the right to assign sublicenses without the written consent of Broad and Harvard. In addition, any sublicense agreements must contain certain terms, including a provision requiring the sublicensee to indemnify Harvard, Broad, MIT, Rockefeller, Iowa and Howard Hughes Medical Institute according to the same terms as are provided in the Cas9 License Agreement and a statement that Broad, Harvard, MIT, Rockefeller, Iowa and Howard Hughes Medical Institute are intended third-party beneficiaries of the sublicense agreement for certain purposes.

We are obligated to use commercially reasonable efforts, or to cause at least one of our affiliates or sublicensees to use commercially reasonable efforts, (i) to research and develop Cas9 licensed products in the licensed field, (ii) to introduce such products in the licensed field into the commercial market, and (iii) to market such products in the licensed field following such introduction into the market and make such products reasonably available to the public. In addition, we, by ourselves or through any of our affiliates or sublicensees, are obligated to achieve certain development milestones within certain time periods. Broad and Harvard have the right to terminate the Cas9 License Agreement if we fail to achieve a development milestone, subject to our right to extend or amend such milestone in accordance with certain procedures. Such termination right will not apply solely with respect to a particular target if, at the time Broad and Harvard elect to terminate the Cas9 License Agreement for failure to achieve a development milestone, we provide evidence reasonably acceptable to Harvard and Broad that we are not in breach of our development milestone diligence obligations with respect to such target and that we are, or one of our affiliates or sublicensees are, (a) researching and developing Cas9 licensed products in the licensed field directed to such target, (b) using commercially reasonable efforts to introduce Cas9 licensed products in the licensed field directed to such target into the commercial market (if applicable), and (c) using commercially reasonable efforts to market Cas9 licensed products in the licensed field directed to such target following such introduction into the market and make such Cas9 licensed products reasonably available to the public (if applicable), and thereafter, for the remainder of the term, we continue, or cause at least one of our affiliates or sublicensees to continue, to develop and commercialize Cas9 licensed products directed to such target in accordance with the foregoing (a)-(c).

Under the Cas9 License Agreement, Broad and Harvard also retained rights to grant further licenses, through its inclusive innovation strategy, under specified circumstances, to third parties, other than specified entities, that wish to develop and commercialize products that target a particular gene outside of the cardiovascular disease field and that otherwise would fall within the scope of our co-exclusive license from Broad and Harvard. If a third party requests a license under the Harvard/Broad Cas9-I Patent Rights for the development and commercialization of a product that would be subject to our co-exclusive license grant from Broad and Harvard under the Cas9 License Agreement, Broad and Harvard may notify us of the request, which we refer to as the Cas9 Third Party Proposed Product Requests. A Cas9 Third Party Proposed Product Request must be accompanied by the third party's bona fide proposal, including the proposed target or category. Broad may not grant a Cas9 Third Party Proposed Product Request (i) if we, directly or indirectly through any of our affiliates or sublicensees, are researching, developing or commercializing a product directed to the same gene target that is the subject of the Cas9 Third Party Proposed Product Request, or the Cas9 Licensee Product, and we can demonstrate such ongoing efforts to Broad's reasonable satisfaction, or (ii) if we, directly or indirectly through any of our affiliates or sublicensees, wish to do so, and we can demonstrate to Broad's reasonable satisfaction that we are interested in researching, developing and commercializing a Cas9 Licensee Product, that we have a commercially reasonable research, development and commercialization plan to do so, and we commence and continue reasonable commercial efforts under such plan. Furthermore, if we, directly or indirectly through any of our affiliates or sublicensees, are not researching, developing or commercializing a Cas9 Licensee Product but wish to grant a sublicense to do so, Broad is obligated to disclose to us the name of the third party and we may enter into a sublicense agreement with the third party. If we, directly or indirectly through any of our affiliates or sublicensees, are not researching, developing or commercializing a Cas9 Licensee Product, are unable to develop and implement a plan reasonably satisfactory to Broad and Harvard, or are unable to enter into a sublicense agreement with the third party, Broad and Harvard have the right to terminate our rights to the specified third-party target or to a specified category and have the right to freely grant to third parties licenses in the licensed field (a) under the patent rights that are exclusively or co-exclusively licensed to us with respect to such specified third party target or (b) under the patent rights that are exclusively or co-exclusively licensed to us within such specified category, provided that such licenses do not grant rights to commercialize products intended for use in the cardiovascular disease field.

Payment terms

Under the Cas9 License Agreement, we paid Broad and Harvard an upfront license fee of $0.1 million and issued an aggregate of 138,037 shares of our common stock to Broad and Harvard. Broad and Harvard also have anti-dilution rights, pursuant to which we (i) have issued Broad and Harvard an aggregate of an additional 309,278 shares of our common stock in the aggregate following the completion of preferred stock financings and (ii) have issued Broad and Harvard an aggregate of an additional 878,098 shares of common stock upon the closing of our IPO.

We also must pay an annual license maintenance fee ranging in dollars from the low- to mid-five figures, depending on the calendar year. A portion of this annual license maintenance fee is creditable against royalties owed on licensed or enabled products in the same year as the maintenance fee is paid.

Broad and Harvard, collectively, are entitled to receive (i) clinical and regulatory milestone payments of up to an aggregate of $5.7 million per licensed product in the United States, the European Union and Japan for the prevention or treatment of a human disease that afflicts fewer than a certain number of patients in the United States and (ii) clinical and regulatory milestone payments of up to an aggregate of $17.4 million per licensed product in the United States, the European Union and Japan for the prevention or treatment of a human disease that afflicts at least a certain number of patients in the United States. If we undergo a change of control during the term of the Cas9 License Agreement, certain of these clinical and regulatory milestone payments will increase by a certain percentage. We are also obligated to make additional payments to Broad and Harvard, collectively, of up to an aggregate of $54.0 million upon the occurrence of certain sales-based milestones per licensed product.

We are also obligated to pay to Broad and Harvard tiered success payments in the event our average market capitalization exceeds specified thresholds ascending from a high nine digit dollar amount to $10.0 billion, or the Market Cap Success Payments, or sale of our company for consideration in excess of those thresholds, or the Company Sale Success Payments, which with the Market Cap Success Payments, we refer to as the Success Payments. Market Cap Success Payments are payable by us in cash, in shares of our common stock, with such shares being valued for such purpose at the closing price of our common stock as reported on the Nasdaq Stock Market for the trading day immediately preceding the date of such payment if our common stock was then listed on the Nasdaq Stock Market, or a combination of shares and cash. In the event of a change of control of our company or a sale of our company, we are required to pay the related Company Sale Success Payment in cash within a specified period following such event. The Success Payments are cumulative and more than one Success Payment may be due and payable based on the average market capitalization on any trigger date. The maximum aggregate Success Payments that could be payable by us are $31.3 million. Certain of the Success Payments are only payable if a licensed product is or has been evaluated in clinical trials. To the extent we issue shares of our common stock in satisfaction of such Success Payments, we will be obligated to file a registration statement with the SEC to register the resale of such shares by Broad and Harvard.

In September 2021, we notified Harvard and Broad that our average market capitalization exceeded three specified thresholds as of a relevant measurement date and aggregate success payments of approximately $6.3 million became payable under the Cas9 License Agreement, which we settled in cash in November 2021.

Broad and Harvard, collectively, are entitled to receive mid single-digit percentage royalties on net sales of licensed products, and low single-digit percentage royalties on net sales of other products enabled by the license, made by us, our affiliates or our sublicensees. The royalty percentage depends on the aggregate amount of the net sales for the licensed or enabled products. If we are legally required to pay royalties to a third party on net sales of our licensed products because such third party holds patent rights that cover such licensed product, then we can credit, subject to a floor, up to a certain percentage of the amount paid to such third party against the royalties due to Broad and Harvard in the same period. On a target-by-target basis, if Editas initiates a program that uses technology covered by the Harvard/Broad Cas Patent Rights and is directed to one of the targets, then the milestone and royalty payments for that specific target shall be reduced by a certain percentage. Our obligation to pay royalties will expire on a product-by-product and country-by-country basis upon the later of (i) the expiration of the last to expire valid claim of the Harvard/Broad Cas9 Patent Rights that cover the composition, manufacture or use of each covered product in each country or (ii) the tenth anniversary of the date of the first commercial sale of the licensed or enabled product. If we sublicense any of the Harvard/Broad Cas9 Patent Rights to a third party, Broad and Harvard, collectively, have the right to receive between 10% and 20% of the sublicense income, which percentage shall decrease to a high single-digit after we meet certain clinical milestones.

Prosecution and enforcement provisions

Broad and Harvard retain control of the prosecution of their respective patent rights. We are obligated to reimburse Broad and Harvard for certain expenses associated with the prosecution and maintenance of the Harvard/Broad Cas9 Patent Rights, including expenses associated with any interference proceedings in the USPTO, any opposition proceedings in the European Patent Office, or any other *inter partes* or other post grant proceedings in these or other jurisdictions where we are seeking patent protection. Broad and Harvard are required to maintain any application or patent within the Harvard/Broad Patents Rights so long as we meet our obligation to reimburse Broad and Harvard for expenses related to prosecution, there is a good faith basis for doing so and doing so is consistent with Broad or Harvard's patent prosecution strategy. If we cease payment for the prosecution of any Harvard/Broad Cas9 Patent Right, then any license granted to us with respect to such Harvard/Broad Cas9 Patent Right will terminate.

We have the first right, but not the obligation, to enforce the Harvard/Broad Cas9-I Patent Rights with respect to our licensed products so long as certain conditions are met, such as providing Broad and Harvard with evidence demonstrating a good faith basis for bringing suit against a third party and subject to coordination with Editas. We are solely responsible for the costs of any lawsuits we elect to initiate and cannot enter into a settlement without the prior written consent of Broad and Harvard (and MIT, Rockefeller and Iowa, if applicable). Any sums recovered in such lawsuits will be shared among us, Broad and Harvard.

Termination provisions

Unless terminated earlier, the term of the Cas9 License Agreement will expire upon the expiration of the last to expire valid claim of the Harvard/Broad Cas9 Patent Rights. However, our royalty and milestone payment obligations, discussed above, may survive expiration or termination. We have the right to terminate the agreement at will upon four months' written notice to Broad and Harvard. Either we or Broad and Harvard may terminate the agreement upon a specified period of notice in the event of the other party's uncured material breach, such notice period varying depending on the nature of the breach. Both Broad and Harvard may terminate the Cas9 License Agreement immediately if we, or our affiliates or sublicensee(s), subject to our ability to cure, challenge the enforceability, validity or scope of any Harvard/Broad Patent Right or assist a third party to do so, or in the event of our bankruptcy or insolvency. Neither Broad nor Harvard acting alone has the right to terminate the Cas9 License Agreement. However, Broad and Harvard may separately terminate the licenses granted to us with respect to their respective patent rights upon the occurrence of the same events that would give rise to the right of both institutions acting collectively to terminate the Cas9 License Agreement.

Collaboration and license agreement with Vertex

On July 18, 2022, we entered into a Strategic Collaboration and License Agreement, or the Vertex Collaboration Agreement, with Vertex for an exclusive, four-year worldwide research collaboration focused on developing *in vivo* gene editing candidates toward an undisclosed target for the treatment of a single liver disease. Additionally, on July 18, 2022, we entered into a Stock Purchase Agreement, or the Stock Purchase Agreement, with Vertex, pursuant to which we agreed to sell and issue shares of our common stock to Vertex in a private placement.

Pursuant to the Vertex Collaboration Agreement, we will be responsible for discovery, research and certain preclinical development of novel *in vivo* gene editing development candidates for the target of interest. Our research activities will be focused on (i) identifying and engineering specific gene editing systems and *in vivo* delivery systems directed to the target and (ii) evaluating and optimizing development candidates to achieve criteria specified in the Vertex Collaboration Agreement. Vertex will reimburse our research expenses consistent with an agreed-upon budget. The research term has an initial term of four years and may be extended by Vertex for up to one additional year.

Vertex will be solely responsible for subsequent development, manufacturing and commercialization of any product candidate resulting from our research efforts. We received an upfront payment from Vertex of $25 million on July 20, 2022. We are eligible to receive (i) success payments of up to $22 million for each product candidate (up to a maximum of $66 million) that achieves the applicable development criteria and (ii) up to an aggregate of $340 million in development and commercial milestone payments. We are also eligible to receive tiered single-digit royalties on net sales, subject to specified reductions. Such royalty payments will terminate on a country-by-country and product-by-product basis upon the later to occur of (i) the expiration of the last to expire valid claim under the patent rights covering such product in such country, (ii) the period of regulatory exclusivity associated with such product in such country or (iii) ten years after the first commercial sale of such product in such country.

Prior to the first patient dosing of the first Phase 1 clinical trial for the first product candidate developed under the Vertex Collaboration Agreement, we also have the right to opt-in to a profit share arrangement pursuant to which

we would share the costs and net profits with Vertex for all product candidates emerging from the collaboration. If we exercise our opt-in right, in lieu of milestones and royalties, we will be obligated to pay for a specified percentage of the development and commercialization costs, and we will have the right to receive a specified percentage of the profits from any sales of any product candidates advanced under the collaboration. At the time we exercise the option, we may elect a profit/cost share of up to 40% (with Vertex retaining a minimum of 60%). In order to exercise our opt-in right, we are required to pay a fee ranging from $25-70 million, depending on the profit/cost percentage elected by us and the licensed technology of Verve included in the most advanced product candidate at the time Verve exercises its opt-in right. Under all profit share scenarios, Vertex will control the worldwide development and commercialization of any product candidates resulting from the collaboration.

The Vertex Collaboration Agreement includes customary representations and warranties, covenants and indemnification obligations for a transaction of this nature. We and Vertex each have the right to terminate the agreement for material breach by, or insolvency of, the other party following notice, and if applicable, a cure period. Vertex may also terminate the Vertex Collaboration Agreement in its entirety for convenience upon 90 days' notice.

In connection with the execution of the Vertex Collaboration Agreement, we also entered into the Stock Purchase Agreement with Vertex for the sale and issuance of 1,519,756 shares of our common stock in a private placement to Vertex at a price of $23.03 per share, which was equal to the five-day volume-weighted average share price as of July 15, 2022, for an aggregate purchase price of $35.0 million. The private placement closed on July 20, 2022.

Government regulation

Government authorities in the United States, at the federal, state and local level and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, sales, 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. The processes for obtaining marketing approvals in the United States and in foreign 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, any product candidates we may develop would be 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 its implementing regulations and guidance. The failure to comply with the applicable U.S. requirements at any time during the product development process, including preclinical testing, clinical testing, the approval process, or post-approval process, may subject a sponsor to delays in the conduct of the study, regulatory review and approval and/or administrative or judicial sanctions.

The FDA must approve a product candidate for a therapeutic indication before it may be marketed in the United States. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products is referred to as a sponsor. A sponsor seeking approval to market and distribute a new biological product in the United States 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 Practices, or GLP regulations;
- completion of the manufacture, under cGMP conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing;
- design of a clinical protocol and its submission to the FDA as part of an IND 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;
- 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 current Good Clinical Practices, or GCP;

- 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 in clinical development and proposed labelling;
- 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;
- satisfactory completion of any FDA audits of the preclinical studies and clinical trial sites to assure compliance with GLP, as applicable, and GCP, and the integrity of clinical data in support of the BLA;
- payment of user Prescription Drug User Fee Act, or PDUFA, securing FDA approval of the BLA and licensure of the new biologic product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies or other post-marketing commitments required by the FDA.

Preclinical studies and investigational new drug application

Before testing any biologic product candidate in humans, 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 animal studies. These studies are typically referred to as IND-enabling studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved new drug application, or NDA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin or recommence.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a partial clinical hold might state that a specific protocol or part of a protocol may not proceed, while other parts of a protocol or other protocols may do so. No more than 30 days after the imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following the issuance of a clinical hold or partial clinical hold, a clinical investigation may only resume once the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed or recommence. Occasionally, clinical holds are imposed due to manufacturing issues that may present safety issues for the clinical study subjects.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all IND requirements must be met unless waived by the FDA. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, the studies must be conducted in accordance with GCP, including undergoing review and receiving approval by an independent ethics committee and seeking and receiving informed consent from subjects. GCP requirements encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data.

Additionally, genetic medicine clinical trials conducted at institutions that receive funding for recombinant DNA research from the U.S. National Institutes of Health, or NIH, also are potentially subject to review by a committee within the NIH's Office of Science Policy called the Novel and Exceptional Technology and Research Advisory Committee, or the NExTRAC. As of 2019, the charter of this review group has evolved to focus public review on clinical trials that cannot be evaluated by standard oversight bodies and pose unusual risks. With certain genetic medicine protocols, FDA review of or clearance to allow the IND to proceed could be delayed if the NExTRAC decides that full public review of the protocol is warranted.

Reporting clinical trial results

Under the PHSA, sponsors of clinical trials of certain FDA-regulated products, including prescription drugs and biologics, are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Although sponsors are also obligated to disclose the results of their clinical trials after completion, disclosure of the results can be delayed in some cases for up to two years after the date of completion of the trial. The NIH's final rule on registration and reporting requirements for clinical trials became effective in 2017, and both the NIH and the FDA have recently signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors.

Specifically, the PHSA grants the Secretary of the U.S. Department of Health and Human Services, or HHS, the authority to issue a notice of noncompliance to a responsible party for failure to submit clinical trial information as required. The responsible party, however, is allowed 30 days to correct the noncompliance and submit the required information. The failure to submit clinical trial information to clinicaltrials.gov, as required, is also a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. In addition to civil monetary penalties, violations may also result in other regulatory action, such as injunction and/or criminal prosecution or disqualification from federal grants. Although the FDA has historically not enforced these reporting requirements due to the HHS's long delay in issuing final implementing regulations, those regulations have now been issued and the FDA has issued several notices of noncompliance since April 2021.

Expanded access to an investigational drug for treatment use

Expanded access, sometimes called "compassionate use," is the use of investigational products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational products for patients who may benefit from investigational therapies. FDA regulations allow access to investigational products under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the investigational product under a treatment protocol or treatment IND application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 trial; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, Fast Track product, or regenerative medicine advanced therapy.

In addition, 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 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 manufacturer to make its investigational products available to eligible patients as a result of the Right to Try Act.

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 or condition to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, 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 any 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. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the trial as support for an IND or application for marketing approval. Specifically, the FDA requires that such trials be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from participants. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for clinical trials in the United States.

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, patient informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or the clinical trial sponsor may suspend or discontinue 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 that the participants are being exposed to an unacceptable health risk. 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 DSMB. This group may recommend continuation of the trial as planned, changes in trial conduct, or cessation of the trial at designated check points based on certain available data from the trial to which only the DSMB has access.

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 more costly Phase 3 clinical trials.
- *Phase 3* clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a biologic; such Phase 3 studies are referred to as "pivotal."

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been

submitted to and reviewed by the FDA. Moreover, as noted above, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate's safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In some cases, the FDA may approve a BLA for a product but require the sponsor to conduct additional clinical trials to further assess the product'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. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement or to request a change in the product labeling. The failure to exercise due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

In December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each phase 3 clinical trial or any other "pivotal study" of a new biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

Interactions with FDA during the clinical development program

Following the clearance of an IND and the commencement of clinical trials, the sponsor will continue to have interactions with the FDA. Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. When clinical data is submitted to support marketing applications, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In addition, sponsors are given opportunities to meet with the FDA at certain points in the clinical development program. Specifically, sponsors may meet with the FDA prior to the submission of an IND, or pre-IND application meeting, at the end of a Phase 2 clinical trial, or EOP2 meeting, and before an NDA or BLA is submitted, or pre-NDA or pre-BLA meeting. Meetings at other times may also be requested. There are four types of meetings that occur between sponsors and the FDA. Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND application and pre-NDA/pre-BLA meetings, as well as Type B end of phase meetings, such as EOP2 meetings. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product. Finally, a type D meeting is focused on a narrow set of issues (should be limited to no more than two focused topics) and should not require input from more than three disciplines or divisions.

These meetings provide an opportunity for the sponsor to share information about the data gathered to date with the FDA and for the FDA to provide advice on the next phase of development. For example, at an EOP2 meeting, a sponsor may discuss its Phase 2 clinical results and present its plans for the pivotal Phase 3 clinical trial(s) that it believes will support the approval of the new product. Such meetings may be conducted in person, via teleconference/videoconference or written response only with minutes reflecting the questions that the sponsor posed to the FDA and the FDA's responses. The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure.

Pediatric studies

Under the Pediatric Research Equity Act of 2003, or PREA, 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. The sponsor must submit an initial pediatric study plan within 60 days of an end-of-phase 2 meeting or as may be agreed between the sponsor and the FDA. 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 sponsor plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The sponsor, 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 sponsor may request an amendment to the plan at any time.

For investigational products intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of a sponsor, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the sponsor, 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. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law now requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response.

Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption in the PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA also maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population.

Special regulations and guidance governing gene therapy products

We expect that the procedures and standards applied to gene therapy products will be applied to any product candidates we may develop. The FDA has defined a gene therapy product as one that seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. 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 CBER, the review of gene therapy and related products is consolidated in the Office of Tissues and Advanced Therapies and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. The NIH, including the NExTRAC, also advises the FDA on gene therapy issues and other issues related to emerging biotechnologies. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols.

The FDA has issued various guidance documents regarding gene therapies, including final guidance documents released in January 2020 relating to chemistry, manufacturing and controls information for gene therapy INDs, long-term follow-up after the administration of gene therapy products, gene therapies for rare diseases and gene therapies for retinal disorders, as well as final guidance in October 2022 for Human Gene Therapy for Neurodegenerative Diseases. Although the FDA has indicated that these and other guidance documents it previously issued are not legally binding, compliance with them is likely necessary to gain approval for any gene therapy product candidate. 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 for potential delayed adverse effects in participants who have received investigational gene therapies with the duration of follow-up based on the potential for risk of such effects. For AAV vectors specifically, the FDA

typically recommends that sponsors continue to monitor participants for potential gene therapy-related adverse events for up to a 5-year period. Other types of gene therapy or gene editing products may require longer follow up, potentially up to a maximum 15-year period.

Compliance with cGMP requirements

Concurrent with clinical trials, companies usually complete additional preclinical studies and must also develop additional information about the physical characteristics of the biologic product candidate as well as finalize a process for manufacturing the product candidate in commercial quantities in accordance with cGMP 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. To help reduce the risk of the introduction of adventitious agents or of causing other adverse events with the use of biologic products, the PHSA emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other requirements, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biologic product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biologic product candidate does not undergo unacceptable deterioration over its shelf life.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug or biologic undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States. Inspections must follow a “risk-based schedule” that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated.

Regulatory requirements governing manufacturing

The FDA’s regulations require that pharmaceutical products be manufactured in specific approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies, and are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. Inspections must follow a “risk-based schedule” that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the NDA sponsor and any third-party manufacturers involved in producing the approved product.

Acceptance and review of a BLA

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product’s chemistry, manufacturing, controls, safety updates, patent information, abuse information and proposed labeling, are submitted to the FDA as part of an application requesting approval to market the product candidate for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product’s use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of a drug product and the safety, potency and purity of the biological product to the satisfaction of the FDA. The fee required for the submission and review of an

application under PDUFA is substantial (for example, for fiscal year 2023 this application fee is approximately $3.3 million), and the sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2023 is more than $394,000 per eligible prescription product. These fees, of which the application fee may be waived for products with orphan drug designation, are typically adjusted annually, and exemptions and waivers may be available under certain circumstances, such as where a waiver is necessary to protect the public health, where the fee would present a significant barrier to innovation, or where the sponsor is a small business submitting its first human therapeutic application for review.

The FDA conducts a preliminary review of all applications within 60 days of receipt and must inform the sponsor by that time whether an application is sufficiently complete to permit substantive review. In pertinent part, the FDA's regulations state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the sponsor. Typically, an RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety, purity and efficacy or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

After the submission is accepted for filing, the FDA begins an in-depth substantive review of the application. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile and whether the product is being manufactured in accordance with cGMP. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application that is a new molecular entity, and six months from the filing date for an application with "priority review." The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission. Despite these review goals, it is not uncommon for FDA review of an application to extend beyond the PDUFA goal date.

In connection with its review of an application, the FDA will typically submit information requests to the sponsor and set deadlines for responses thereto. The FDA will also conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether the manufacturing processes and facilities comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and are adequate to assure consistent production of the product within required specifications.

The FDA also may inspect the sponsor and one or more clinical trial sites to assure compliance with IND applications and GCP requirements and the integrity of the clinical data submitted to the FDA. With passage of FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to FDA as well as other persons holding study records or involved in the study process. To ensure cGMP and GCP compliance by its employees and third-party contractors, a sponsor may incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Additionally, the FDA may refer an application, including applications for novel product candidates which present difficult questions of safety or efficacy, to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. 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 recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. Data from clinical trials are not always conclusive, and the FDA or its advisory committee may interpret data differently than the sponsor interprets the same data. The FDA may also re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the sponsor during the review process.

The FDA also may require submission of a REMS if it determines that a REMS is necessary to ensure that the benefits of the product outweigh its risks and to assure the safe use of the product. The REMS could include medication guides, physician communication plans, assessment plans and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. The FDA determines the

requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS and the FDA will not approve the application without a REMS.

Decisions on BLAs

The FDA reviews an application to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The term "substantial evidence" is defined under the FDCA as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product involved, on the basis of which it could fairly and responsibly be concluded by such experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical investigations to establish effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard. This approach was subsequently endorsed by Congress in 1998 with legislation providing, in pertinent part, that "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence." This modification to the law recognized the potential for the FDA to find that one adequate and well controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. In December 2019, the FDA issued draft guidance further explaining the studies that are needed to establish substantial evidence of effectiveness. It has not yet finalized that guidance.

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a CRL or an approval letter. To reach this determination, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the NDA or BLA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks. In connection with this assessment, the FDA review team will assemble all individual reviews and other documents into an "action package," which becomes the record for the FDA's review. The FDA review team then issues a recommendation, and a senior FDA official makes a decision.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time- consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six month extension to respond. The FDA has committed to reviewing such resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. The FDA has taken the position that a CRL is not final agency action making the determination subject to judicial review.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. That is, the approval will be limited to the conditions of use (e.g., patient population and indication) described in the FDA-approved labeling. Further, depending on the specific risk(s) to be addressed, the FDA may require that contraindications, warnings, or precautions be included in the product labeling; post-approval trials, including Phase 4 clinical trials, be conducted to further assess a product's safety after approval; and/or testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing trials or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Under the Ensuring Innovation Act, which was signed into law in April 2021, the FDA must publish action packages summarizing its decisions to approve new drugs and biologics within 30 days of approval of such products. To date, CRLs are not publicly available documents.

Expedited review programs

The FDA is authorized to expedite the review of BLAs in several ways. Under the Fast Track program, the sponsor of a product candidate may request the FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND. Candidate products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with the FDA, the FDA may initiate review of sections of a Fast Track application before the application is complete, a process known as rolling review.

Any product candidate submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority review, accelerated approval or regenerative medicine advanced therapy designation.

- *Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.
- *Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention compared to marketed products. The FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.
- *Accelerated approval.* Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.

With passage of FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to the FDA every six months until the study is completed; and use expedited procedures to withdraw accelerated approval of an NDA or BLA after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

- *Regenerative medicine advanced therapy.* With passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative 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 candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the 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.

None of these expedited programs changes the standards for approval but they may help expedite the development or approval process of product candidates.

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 have 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 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 and standards 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 include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about a product;
- mandated modification of promotional materials and labeling and issuance of corrective information;
- fines, 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 recall, seizure or detention, or refusal to permit the import or export of products;
- injunctions or the imposition of civil or criminal penalties; and
- consent decrees, corporate integrity agreements, debarment, or exclusion from federal health care programs.

Pharmaceutical products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Although healthcare providers may prescribe products for uses not described in the drug's labeling, known as off-label uses, in their professional judgment, drug manufacturers are prohibited from soliciting, encouraging or promoting unapproved uses of a product. 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.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In September 2021, the FDA published final regulations that describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic.

It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Moreover, with passage of the Pre-Approval Information Exchange Act, in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

Finally, if there are any modifications to the product, including changes in indications, labeling or manufacturing processes or facilities, the sponsor may be required to submit and obtain FDA approval of a new BLA or a BLA supplement, which may require the sponsor to develop additional data or conduct additional preclinical studies and clinical trials. Securing FDA approval for new indications is similar to the process for approval of the original indication and requires, among other things, submitting data from adequate and well-controlled clinical trials to demonstrate the product's safety and efficacy in the new indication. Even if such trials are conducted, the FDA may not approve any expansion of the labeled indications for use in a timely fashion, or at all. There also are continuing, annual user fee requirements that are now assessed as program fees for certain approved drugs.

Orphan drug designation and exclusivity

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for treatment of 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 at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process 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.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same product for the same indication for seven years, except in certain limited circumstances. If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

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. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of the FDA Reauthorization Act of 2017, but have not yet been approved or licensed by the FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of exclusivity, the term “same disease or condition” in the statute means the designated “rare disease or condition” and could not be interpreted by the FDA to mean the “indication or use.” Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the “indication or use.” Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

Pediatric exclusivity

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 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 non-patent exclusivity that cover the product are extended by six months.

Regulatory exclusivity governing biologics

When a biological product is licensed for marketing by the FDA with approval of a BLA, the product may be entitled to certain types of market and data exclusivity barring the FDA from approving competing products for certain periods of time. In March 2010, the Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the PPACA, was enacted in the United States and included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or the BPCIA. The BPCIA amended the PHSA to create an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. To date, the FDA has approved a number of biosimilars and the first interchangeable biosimilar product was approved on July 30, 2021 and a second product previously approved as a biosimilar was designated as interchangeable in October 2021. The FDA has also issued numerous guidance documents outlining its approach to reviewing and licensing biosimilars and interchangeable biosimilars under the PHSA, including a draft guidance issued in November 2020 that seeks to provide additional clarity to manufacturers of interchangeable biosimilars.

Under the BPCIA, a manufacturer may submit an application for a product that is “biosimilar to” a previously approved biological product, which the statute refers to as a “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 the proposed biosimilar product in terms of safety, purity and potency. The biosimilar sponsor may demonstrate that its product is biosimilar to the reference product on the basis of data from analytical studies, animal studies and one or more clinical studies to demonstrate safety, purity and potency in one or more appropriate conditions of use for which the reference product is approved. In addition, the sponsor must show that the biosimilar and reference products have the same mechanism of action for the conditions of use on the label, route of administration, dosage and strength, and the production facility must meet standards designed to assure product safety, purity and potency.

For the FDA to approve a biosimilar product as interchangeable with a reference product, the FDA must find not only that the product is biosimilar to the reference product but also that it can be expected to produce the same clinical results as the reference product such that the two products may be switched without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. Upon licensure by the FDA, an interchangeable biosimilar may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. Following approval of the interchangeable biosimilar product,

the FDA may not grant interchangeability status for any second biosimilar until one year after the first commercial marketing of the first interchangeable biosimilar product. In December 2022, Congress clarified through FDORA that the FDA may approve multiple first interchangeable biosimilar biological products so long as the products are all approved on the first day on which such a product is approved as interchangeable with the reference product.

A reference biological product is granted 12 years of exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference product until four years after the date of first licensure of the reference product. Even if a product is considered to be a reference product eligible for exclusivity, however, 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. There have been recent government proposals to reduce the 12-year reference product exclusivity period, but none has been enacted to date. At the same time, since the passage of the BPCIA, many states have passed laws or amendments to laws that address pharmacy practices involving biosimilar products.

Patent term restoration and extension

In the United States, a patent claiming a new biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent extension of up to five years for patent term lost during product development and FDA regulatory review. Assuming grant of the patent for which the extension is sought, the restoration period for a patent covering a product is typically one-half the time between the effective date of the IND application and the submission date of the BLA, plus the time between the submission date of the BLA and the ultimate approval date. 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 in the United States. 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 for which extension is sought. 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 in consultation with the FDA.

Federal and state data privacy and security laws

There are multiple privacy and data security laws that may impact our business activities, in the United States and other countries where we conduct our trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, under the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, the HHS has issued regulations to protect the privacy and security of protected health information, or PHI, used or disclosed by covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also regulates standardization of data content, codes and formats used in healthcare transactions and standardization of identifiers for health plans and providers. HIPAA also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. HIPAA may apply to us in certain circumstances and may also apply to our business partners in ways that may impact our relationships with them. Our clinical trials will be regulated by HIPAA's Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. State attorneys general also have authority to enforce state privacy and security laws. New laws and regulations governing privacy and security may be adopted in the future as well.

At the state level, California has enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Additionally, effective starting on January 1, 2023, the California Privacy Rights Act, or CPRA, will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA

and the CPRA. The CCPA and CPRA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and individually identifiable health information. These provisions may apply to some of our business activities. In addition, other states, including Virginia and Colorado, have already passed state privacy laws and other states will likely be considering similar laws in the near future.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our current or future business activities, including certain clinical research, sales and marketing practices and the provision of certain items and services to our customers, could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that a healthcare company may fail to comply fully with one or more of these requirements. If our operations are found to be in violation of any of the privacy or data security laws or regulations described above that are applicable to us, or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil and administrative penalties, damages, fines, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any product candidates we may develop, once approved, are sold in a foreign country, we may be subject to similar foreign laws.

FDA approval of companion diagnostics

In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. In July 2016, the FDA issued a draft guidance intended to assist sponsors of the drug therapeutic and in vitro companion diagnostic device on issues related to co-development of the products.

The 2014 guidance also explains that a companion diagnostic device used to make treatment decisions in clinical trials of a biologic product candidate generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption, or IDE, regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a product are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the study plan and subjects, a sponsor may seek to submit an IND alone, or both an IND and an IDE.

In April 2020, the FDA issued additional guidance that describes considerations for the development and labeling of companion diagnostic devices to support the indicated uses of multiple drug or biological oncology products, when appropriate. This guidance builds upon existing policy regarding the labeling of companion diagnostics. In its 2014 guidance, the FDA stated that if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group of therapeutic products, the companion diagnostic's intended use or indications for use should name the specific group of therapeutic products, rather than specific products. The 2020 guidance expands on the policy statement in the 2014 guidance by recommending that companion diagnostic developers consider a number of factors when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support a broader labeling claim such as use with a specific group of oncology therapeutic products (rather than listing an individual therapeutic product(s)).

Under the FDCA, in vitro diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import and post-market surveillance. Unless an exemption applies, diagnostic tests require pre-notification marketing clearance or approval from the FDA prior to commercial distribution.

The FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. For federal fiscal year 2023, the standard fee is $441,547 and the small business fee is $110,387.

Regulation and procedures governing approval of medicinal products in the European Union

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, a sponsor will need to obtain the necessary approvals by the comparable foreign 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 the European Union generally follows the same lines as in the United States. It 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 relevant competent authorities of an MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical trial approval

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014. That regulation became effective on January 31, 2022, following confirmation of full functionality of the Clinical Trials Information System through an independent audit by the European Commission in mid-2020.The Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include a streamlined application procedure via a single entry point, the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all European Union member states in which an application for authorization of a clinical trial has been submitted (member states concerned). Part II is assessed separately by each member state concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned European Union member states. However, overall related timelines will be defined by the Clinical Trials Regulation.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the European Union at the EudraCT website: https://eudract.ema.europa.eu.

PRIME designation in the European Union

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. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies are appointed early in the PRIME scheme facilitating increased understanding of the product at the EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing authorization

To obtain a marketing authorization for a product under the European Union regulatory system, a sponsor must submit an MAA, either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in European Union member states (decentralized procedure, national

procedure, or mutual recognition procedure). A marketing authorization may be granted only to a sponsor established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, a sponsor 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 for all European Union member states. 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 products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. Manufacturers must demonstrate the quality, safety and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Specifically, the grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, 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 1394/2007/EC 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 EMA which provides an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

Under the centralized procedure, the CHMP established at the EMA is responsible for conducting an initial assessment of a product. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is 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 limit of 210 days will be reduced to 150 days, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that it is no longer appropriate to conduct an accelerated assessment.

National Authorization Procedures

There are also two other possible routes to authorize medicinal products in several European Union member states, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- *Decentralized procedure*. Using the decentralized procedure, a sponsor may apply for simultaneous authorization in more than one European Union member state of medicinal products that have not yet been authorized in any European Union member state and that do not fall within the mandatory scope of the centralized procedure. The sponsor may choose a European Union member state as the reference member state to lead the scientific evaluation of the application.
- *Mutual recognition procedure*. In the mutual recognition procedure, a medicine is first authorized in one European Union member state (which acts as the reference member state), in accordance with the national procedures of that member state. Following this, further marketing authorizations can be progressively sought from other European Union member states in a procedure whereby the members concerned agree to recognize the validity of the original, national marketing authorization produced by the reference European Union member state.

Under the above-described procedures, before granting the marketing authorization, the EMA or the competent authorities of the European Union member state of the European Economic Area, or the EEA, make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Conditional Approval

In specific circumstances, E.U. legislation (Article 14–a Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizations for Medicinal Products for Human Use) enables sponsors to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the product candidate is intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases; (2) the product candidate is intended to meet unmet medical needs of patients; (3) a marketing authorization may be granted prior to submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required; (4) the risk-benefit balance of the product candidate is positive, and (5) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Specialized procedures for gene therapies

The grant of marketing authorization in the European Union for gene therapy products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, 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 1394/2007/EC includes specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Pediatric studies

Prior to obtaining a marketing authorization in the European Union, sponsors must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are provided in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

Regulatory data protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon 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 regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent term extensions in the European Union and other jurisdictions

The European Union also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

Periods of authorization and renewals

A 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 member state. To that end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. 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 placement of the drug on the European Union market (in the case of the centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

Regulatory requirements after marketing authorization

Following approval, 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 European Union'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 EMA's GMP requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. 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 European Union under Directive 2001/83EC, as amended.

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 the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the drug in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the sponsor must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the drug 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 possibility to apply for a centralized European Union marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for 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.

Pediatric exclusivity

If a sponsor obtains a marketing authorization in all European Union member states, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate, or SPC.

Approval of companion diagnostic devices

In the European Union, medical devices such as companion diagnostics must comply with the General Safety and Performance Requirements, or SPRs, detailed in Annex I of the EU Medical Devices Regulation (Regulation (EU) 2017/745), or MDR, which came into force on May 26, 2021 and replaced the previously applicable EU Medical Devices Directive (Council Directive 93/42/EEC). Compliance with SPRs and additional requirements applicable to companion medical devices is a prerequisite to be able to affix the Conformitè Europëenne mark of conformity to medical devices, without which they cannot be marketed or sold. To demonstrate compliance with the SPRs, a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. The MDR is meant to establish a uniform, transparent, predictable, and sustainable regulatory framework across the European Union for medical devices.

Separately, the regulatory authorities in the European Union also adopted a new In Vitro Diagnostic Regulation (Regulation (EU) 2017/746), which became effective in May 2022. The new regulation replaces the In Vitro Diagnostics Directive (IVDD) 98/79/EC. Manufacturers wishing to apply to a notified body for a conformity assessment of their in vitro diagnostic medical device had until May 2022 to update their technical documentation to meet the requirements and comply with the new, more stringent regulation. The new regulation will, among other things:

- strengthen the rules on placing devices on the market and reinforce surveillance once they are available;
- establish explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance and safety of devices placed on the market;
- improve the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number;
- set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the European Union; and
- strengthen rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Brexit and the regulatory framework in the United Kingdom

The United Kingdom's withdrawal from the European Union took place on January 31, 2020. The European Union and the United Kingdom reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the Agreement, which was applied provisionally beginning on January 1, 2021 and which entered into force on May 1, 2021. The Agreement focuses primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the European Union and the United Kingdom will form two separate markets governed by two distinct regulatory and legal regimes. As such, the Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the United Kingdom is no longer part of the single market. As of January 1, 2021, the MHRA became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law, the body of EU law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union.

Since a significant proportion of the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom. For example, the United Kingdom is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the

United Kingdom. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure.

Also, notwithstanding the United Kingdom's withdrawal from the European Union, by operation of the so-called 'UK GDPR' (i.e., the EU General Data Protection Regulation, or GDPR, as it continues to form part of the law of the United Kingdom by virtue of section 3 of the EU (Withdrawal) Act 2018 and as subsequently amended) the GDPR continues to apply in substantially equivalent form to processing operations carried out in the context of an establishment in the United Kingdom and any processing relating to the offering of goods or services to individuals in the United Kingdom and/or monitoring of their behavior in the United Kingdom.

However, it is still unclear whether transfers of data from the EEA to the United Kingdom will remain lawful under the GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the UK will be treated like a European Union member state in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a "third country" under the GDPR (and transfers of data from the EEA to the United Kingdom will require a 'transfer mechanism' such as the Standard Contractual Clauses) unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the United Kingdom. While the European Commission has published draft adequacy decisions in respect of the United Kingdom, these are subject to further review and it remains to be seen whether or when any such decisions will be adopted. The UK government has already determined that it considers all European Union and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the European Union and EEA remain unaffected. We may, however, incur liabilities, expenses, costs and other operational losses under GDPR and applicable European Union member states and the United Kingdom privacy laws in connection with any measures we take to comply with them. Furthermore, in general terms, there will now be increasing scope for divergence in application, interpretation and enforcement of the data protection law as between the United Kingdom and EEA.

General Data Protection Regulation

The collection, use, disclosure, transfer or other processing of personal data in the context of the activities of an establishment in the EEA and/or regarding the offering of goods or services to, and/or the monitoring of the behavior of individuals in the EEA, including health data, is subject to the GDPR, which became effective on May 25, 2018. As noted above, by operation of the so-called 'UK GDPR,' the GDPR continues to apply in substantially equivalent form in the context of the UK, UK establishments and UK-focused processing operations—so, when we refer to the GDPR in this section, we are also making reference to the UK GDPR in the context of the United Kingdom, unless the context requires otherwise.

The GDPR is wide-ranging in scope and imposes numerous, significant and complex requirements on companies that process personal data, such as: requiring the establishment of a legal basis for processing personal data; broadening the definition of personal data (including to capture 'pseudonymized' or key-coded data that is commonly processed in a clinical trial-related context); creating obligations for controllers and processors to appoint data protection officers in certain circumstances; increasing transparency obligations to data subjects; establishing limitations on the retention of personal data; introducing obligations to honor increased rights for data subjects; formalizing a heightened standard of data subject consent; establishing obligations to implement certain technical and organizational safeguards to protect the security and confidentiality of personal data; introducing obligations to agree to certain specific contractual terms and to take certain measures when working with third-party processors or joint controllers; introducing the obligation to provide notice of certain significant personal data breaches to the relevant supervisory authority(ies) and affected individuals; and mandating the appointment of representatives in the United Kingdom and/or European Union in certain circumstances. In particular, the processing of "special category personal data" (such as personal data related to health and genetic information), which will be relevant to our operations in the context of clinical trials, imposes heightened compliance burdens under the GDPR and is a topic of active interest among relevant regulators. In addition, the GDPR provides that EEA member states may introduce specific requirements related to the processing of special categories of personal data such as health data that we may process in connection with clinical trials or otherwise. In the United Kingdom, the UK Data Protection Act 2018 complements the UK GDPR in this regard. More broadly, European data protection authorities may interpret the GDPR and national laws differently and impose additional requirements, which contributes to the complexity of processing personal data in or from the EEA and/or United Kingdom. Guidance on implementation and compliance practices is often updated or otherwise revised. This fact may lead to greater divergence on the law that applies to the processing of personal data across the EEA and/or United Kingdom, which may increase our costs and overall compliance risk. Such country-specific regulations could also limit our ability to process relevant personal data in the context of our EEA and/or United Kingdom

operations ultimately having an adverse impact on our business, and harming our business and financial condition.

The GDPR also imposes strict rules on the transfer of personal data to countries outside Europe, including to the United States, unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. Certain previously available safeguards have been invalidated, and reliance on alternative safeguards may be complex or not possible in certain circumstances, following a recent ruling of the Court of Justice of the European Union and subsequent regulatory guidance. If we are unable to implement a valid solution for personal data transfers from the EEA and United Kingdom, including, for example, obtaining individuals' explicit consent to transfer their personal data to the United States or other countries, we will face increased exposure to regulatory actions, substantial fines and injunctions against transferring personal data from the EEA and United Kingdom. Inability to export personal data from the EEA and United Kingdom may also restrict our activities outside the EEA and United Kingdom; limit our ability to collaborate with partners as well as other service providers, contractors and other companies outside of the EEA and United Kingdom; and/or require us to increase our processing capabilities within the EEA and/or United Kingdom at significant expense or otherwise cause us to change the geographical location or segregation of our relevant systems and operations—any or all of which could adversely affect our operations or financial results. Additionally, other countries outside of the EEA and United Kingdom have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of delivering our services and operating our business.

The GDPR also provides for more robust regulatory enforcement and permits supervisory authorities to impose greater penalties for violations than under previous European data protection laws, including potential fines of up to €20 million or 4% of annual global revenues for the preceding financial year, whichever is greater. In addition to administrative fines, a wide variety of other potential enforcement powers are available to supervisory authorities in respect of potential and suspected violations of the GDPR, including extensive audit and inspection rights, and powers to order temporary or permanent bans on all or some processing of personal data carried out by noncompliant actors. 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.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-US Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the European Union.

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 payers 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 payers, 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. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the product once coverage is approved. Third-party payers 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 payers 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 payer 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 payer's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payer's determination to provide coverage for a product does not assure that other payers will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payer to payer. 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. In addition, any companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or biological products, will apply to any companion diagnostics.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceuticals have been a focus in this effort. Governments 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.

If we obtain approval in the future to market in the United States any product candidates we may develop, we may be required to provide discounts or rebates under government healthcare programs or to certain government and private purchasers in order to obtain coverage under federal healthcare programs such as Medicaid. Participation in such programs may require us to track and report certain drug prices. We may be subject to fines and other penalties if we fail to report such prices accurately.

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 European Union, 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) in order to obtain reimbursement or pricing approval. For example, the European Union 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. European Union 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 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 European Union have increased the amount of discounts required on 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 European Union. The downward pressure on healthcare 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 European Union member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. 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

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug 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, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements.

Restrictions under applicable federal and state health care laws and regulations include the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, 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 health care program such as Medicare and Medicaid; the federal civil and criminal false claims laws, including the civil 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 made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government; HIPAA, which created additional federal criminal statutes that prohibit, among other things, a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services; the Foreign Corrupt Practices Act, or FCPA, which 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 the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within HHS, information related to payments and other transfers of value made by that entity to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members, and, as of 2022, will require applicable manufacturers to report information regarding payments and other transfers of value provided during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants, and certified nurse midwives.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign 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.

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.

In March 2010, the United States Congress enacted the PPACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, 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 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to two percent per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, and subsequent legislation, these Medicare sequester reductions were suspended and reduced through June 2022,with the full 2% cut remaining thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, the Tax Act repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Pharmaceutical prices

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, presidential executive orders, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the prices of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the prices of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, the HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Medicare Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2032 by the Inflation Reduction Act.

On July 9, 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The order directs the HHS to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." On September 9, 2021, the HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic pharmaceuticals, and increase transparency; and foster scientific innovation to

promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least nine years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

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. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional health care organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription pharmaceutical 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.

Employees and human capital resources

As of December 31, 2022, we had 204 full-time employees, including 58 employees with M.D., Pharm.D. or Ph.D. degrees. Of these full-time employees, 164 are engaged in research and development activities and 40 are engaged in general and administrative activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

We have attracted a diverse team of experts in discovery, preclinical research and clinical development, as well as gene editing technologies and the manufacturing and delivery of genetic medicines. Our team is built on several core values that drive our day-to-day activities and inspire our long-term vision:

- Grit: we work tenaciously to solve problems and advance science with rigor and care.
- Spirit: we act with integrity and inclusion to earn the trust of colleagues, partners, patients and providers.
- Drive: we enthusiastically pursue our potential, and we empower those around us to do the same.
- Passion: we are motivated by our mission to reimagine the approach to the treatment of CVD for patients and their families.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. We are committed to diversity, equity and inclusion across all aspects of our organization, including in our recruitment, advancement and development practices. Each year, we

review employee demographic information to evaluate our diversity efforts across all functions and levels of the company. We conduct annual performance and development reviews for each of our employees to discuss the individual's strengths and development opportunities, career development goals and performance goals. We also regularly survey employees to assess employee engagement and satisfaction. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees and directors through the granting of stock-based compensation awards. We value our employees and regularly benchmark total rewards we provide, such as short-and long-term compensation, 401(k) contributions, health, welfare and quality of life benefits, paid time off and personal leave, against our industry peers to ensure we remain competitive and attractive to potential new hires.

Our Corporate Information

We were incorporated under the laws of the state of Delaware on March 9, 2018 under the name Endcadia, Inc. On January 15, 2019, we changed our name to Verve Therapeutics, Inc.

Our principal executive office is located at 201 Brookline Avenue, Suite 601, Boston, Massachusetts 02215 and our telephone number is (617) 603-0070. Our website address is http://www.vervetx.com. The information contained on, or accessible through, our website does not constitute part of this Annual Report. We have included our website address in this Annual Report solely as an inactive textual reference.

Available Information

Our Internet address is http://www.vervetx.com. 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 through the "Investors" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or SEC. Information on our website is not part of this Annual Report or any of our other securities filings unless specifically incorporated herein by reference. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at http://www.sec.gov. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

Item 1A. Risk Factors.

Our future operating results could differ materially from the results described in this Annual Report on Form 10-K due to the risks and uncertainties described below. You should consider carefully the following information about risks below in evaluating our business. If any of the following risks actually occur, our business, financial conditions, results of operations and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock would likely decline. In addition, we cannot assure investors that our assumptions and expectations will prove to be correct. Important factors could cause our actual results to differ materially from those indicated or implied by forward-looking statements. See page 3 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. Factors that could cause or contribute to such differences include those factors discussed below.

Risks related to our financial position and need for additional capital

We have incurred significant losses since our inception and have no products approved for sale. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

Since our inception, we have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials, and have incurred significant operating losses. Our net losses were $157.4 million, $120.3 million and $45.7 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $344.2 million. We have not generated any revenue from product sales. We have financed our operations primarily through private placements of our preferred stock and common stock and from the sale of common stock in public offerings and payments received in connection with the Strategic Collaboration and License Agreement, or the Vertex Agreement, with Vertex Pharmaceuticals Incorporated, or Vertex, in July 2022.

We expect to continue to incur significant operating expenses and net losses for the foreseeable future. Our operating expenses and net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if and as we:

- conduct our ongoing heart-1 clinical trial for VERVE-101 in New Zealand and the United Kingdom, and if our investigational new drug application, or IND, is cleared, in the United States;
- continue our current research programs and our preclinical development of product candidates;
- seek to identify additional research programs and additional product candidates;
- advance our existing and future product candidates into clinical development;
- initiate preclinical studies and clinical trials for any additional product candidates we identify and develop or expand development of existing programs into additional patient populations;
- maintain, expand, enforce, defend and protect our intellectual property portfolio and provide reimbursement of third-party expenses related to our patent portfolio;
- seek regulatory and marketing approvals for any of our product candidates that we develop;
- perform research services under the Vertex Agreement and seek to identify, establish and maintain additional collaborations and license agreements, and the success of those collaborations and license agreements;
- make milestone payments to Beam Therapeutics Inc., or Beam, under our amended and restated collaboration and license agreement with Beam, or the Beam Agreement, milestone payments to Acuitas Therapeutics Inc., or Acuitas, under our non-exclusive license agreement with Acuitas, or the Acuitas Agreement, milestone payments or success payments to The Broad Institute, Inc., or Broad, and the President and Fellows of Harvard College, or Harvard, under our license agreement with Broad and Harvard (as amended, the Cas9 License Agreement), and milestone payments to Novartis Pharma AG, or Novartis, under our license agreement with Novartis, or the Novartis Agreement, and potential payments to other third parties under our other collaboration agreements or any additional future collaboration or license agreements that we obtain;
- ultimately establish a sales, marketing, and distribution infrastructure to commercialize any drug products for which we may obtain marketing approval, either by ourselves or in collaboration with others;
- further develop our base editing technology and develop novel gene editing technology;
- hire additional personnel including research and development, clinical and commercial personnel;

- add operational, financial and management information systems and personnel, including personnel to support our product development;
- acquire or in-license products, intellectual property, medicines and technologies;
- satisfy any post-approval marketing requirements, such as a cardiovascular outcomes trial, or CVOT, which we expect will be required for VERVE-101 and VERVE-201;
- establish commercial-scale current good manufacturing practices, or cGMP, capabilities through a third-party or our own manufacturing facility; and
- continue to operate as a public company.

In addition, our expenses will further increase if, among other things:

- we are required by the U.S. Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform clinical trials or preclinical studies that are in addition to, or different than, those expected;
- there are any delays in completing our clinical trials or preclinical studies or the development of any of our product candidates; or
- there are any third-party challenges to our intellectual property or we need to defend against any intellectual property-related claim.

Even if we obtain marketing approval for, and are successful in commercializing, one or more of our product candidates, we expect to incur substantial additional research and development and other expenditures to develop and market additional product candidates and/or to expand the approved indications of any marketed product. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue.

We have never generated revenue from product sales and may never achieve or maintain profitability.

We have only recently initiated clinical development of our first product candidate and expect that it will be many years, if ever, before we have a product candidate ready for commercialization. To become and remain profitable, we must succeed in developing, obtaining the necessary regulatory approvals for and eventually commercializing a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including:

- completing preclinical testing and clinical trials;
- identifying additional product candidates;
- obtaining marketing approval for these product candidates;
- manufacturing, marketing and selling any products for which we may obtain marketing approval; and
- achieving market acceptance of products for which we may obtain marketing approval as viable treatment options.

We are only in the preliminary stages of these activities and there is no assurance that we will be successful in these activities and, even if we are, may never generate revenues that are significant enough to achieve profitability. We have not yet completed a clinical trial of any product candidate. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to generate revenue or achieve profitability.

Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement, and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect to devote substantial financial resources to our ongoing and planned activities, particularly as we conduct our ongoing Phase 1b clinical trial of VERVE-101, complete preclinical studies of VERVE-201, continue research, development and preclinical testing, initiate additional clinical trials and potentially seek marketing approval for VERVE-101, VERVE-201, and any other product candidates we may develop. We expect our expenses to increase substantially in connection with our ongoing and planned activities, particularly as we advance our preclinical activities and our ongoing and planned clinical trials. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. We currently do not have a credit facility or any committed sources of capital. If we are unable to raise capital or obtain adequate funds when needed or on acceptable terms, we may be forced to delay, limit, reduce or terminate our research and development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future capital requirements will depend on many factors, including:

- the progress, costs and results of our ongoing Phase 1b clinical trial of VERVE-101 and any future clinical development of VERVE-101;
- the scope, progress, results and costs of discovery, preclinical and clinical development for any product candidates we may develop;
- the costs of developing or acquiring licenses for the delivery modalities that will be used with our future product candidates;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims, including claims of infringement, misappropriation or other violation of third-party intellectual property;
- the costs, timing and outcome of regulatory review of the product candidates we may develop;
- the costs of future commercialization activities, either by ourselves or in collaboration with others, including product sales, marketing, manufacturing, and distribution for any product candidates for which we receive marketing approval;
- the costs of satisfying any post-approval marketing requirements, such as a CVOT;
- the revenue, if any, received from commercial sales of product candidates we may develop for which we receive marketing approval;
- the success of our license agreements and our collaborations;
- 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 collaboration or license agreements we enter into;
- the extent to which we acquire or in-license products, intellectual property and technologies;
- the costs of operational, financial and management information systems and associated personnel; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, even if we successfully identify and develop product candidates and those are approved, we may not achieve commercial success. Our commercial revenues, if any, may not be sufficient to sustain our operations. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of approximately $554.8 million. We believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2025. However, we have based

this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of many factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect and could be forced to seek additional funding sooner than planned.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize any product candidates. We cannot be certain that additional funding will be available on acceptable terms, or at all. For example, economic and other factors have recently caused significant disruption of global financial markets, which could continue and would reduce our ability to access capital, which could in the future negatively affect our liquidity. We have no committed source of additional capital or external funds and, if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. We could be required to seek collaborators for product candidates we may develop at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to product candidates we may develop in markets where we otherwise would seek to pursue development or commercialization ourselves.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial revenues from product sales, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any source of committed capital or external funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights as a common stockholder. Any debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures, declaring dividends or encumbering our assets to secure future indebtedness.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs 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 or other arrangements when needed or on terms acceptable to us, we would 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.

Our limited operating history may make it difficult for stockholders to evaluate the success of our business to date and to assess our future viability.

We commenced operations in 2018 and are a clinical-stage company. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential product candidates, securing intellectual property rights, conducting preclinical studies and an early-stage clinical trial. We initiated our first clinical trial, a Phase 1b clinical trial for VERVE-101, in July 2022. Our other research programs, including VERVE-201, are still in the research or preclinical stage of development, and their risk of failure is high. We have not yet demonstrated our ability to complete any clinical trials, obtain marketing approvals, manufacture a clinical development or commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. In part because of this lack of experience, we cannot be certain that our ongoing preclinical studies and clinical trial will be completed on time or if the planned preclinical studies and clinical trials will begin or be completed on time, if at all. Consequently, any predictions stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing gene editing products.

Our limited operating history, particularly in light of the rapidly evolving genetic medicines field, may make it difficult to evaluate our technology and industry and predict our future performance. Our limited 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.

In addition, as our business grows, we may encounter unforeseen expenses, restrictions, difficulties, complications, delays and other known and unknown factors. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Our ability to use our net operating losses and research and development tax credit carryforwards to offset future taxable income or taxes may be subject to certain limitations.

We have a history of cumulative losses and anticipate that we will continue to incur significant losses in the foreseeable future; thus, we do not know whether or when we will generate taxable income necessary to utilize our net operating losses, or NOLs, or research and development tax credit carryforwards. As of December 31, 2022, we had federal NOL carryforwards of $173.6 million and state NOL carryforwards of $157 million.

In general, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, a corporation that undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three-year period, is subject to limitations on its ability to utilize its pre-change NOLs and research and development tax credit carryforwards to offset post-change taxable income or taxes. We have not conducted a study to assess whether any such ownership changes have occurred. We may have experienced such ownership changes in the past and may experience such ownership changes in the future as a result of subsequent changes in our stock ownership (which may be outside our control). As a result, if, and to the extent that, we earn net taxable income, our ability to use our pre-change NOLs and research and development tax credit carryforwards to offset such taxable income may be subject to limitations. Our NOLs or credits may also be impaired under state law.

There is also a risk that due to regulatory changes, such as suspensions on the use of NOLs, or other unforeseen reasons, our existing NOLs could expire or otherwise become unavailable to offset future income tax liabilities. As described below in "Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the Tax Cuts and Jobs Act, or the Tax Act, as amended by the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, included changes to U.S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future. For these reasons, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes.

Risks related to discovery and development

We are very early in our development efforts, and we have not yet completed a clinical trial of any product candidate. As a result, we expect it will be many years before we commercialize any product candidate, if ever. If we are unable to advance our current or future product candidates through clinical trials, obtain marketing approval and ultimately commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts and have focused our efforts to date primarily on research efforts and preclinical development. We initiated our first clinical trial, a Phase 1b clinical trial for VERVE-101 in July 2022, but we have not yet completed a clinical trial of any product candidate Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development, marketing approval and eventual commercialization of our product candidates, which may never occur. We have not yet generated revenue from product sales, and we may never be able to develop or commercialize a marketable product.

Commencing clinical trials in the United States is subject to acceptance by the FDA of an IND and finalizing the trial design based on discussions with the FDA and other regulatory authorities.

The FDA or other regulatory agencies may require us to complete additional preclinical studies or require us to satisfy other requests prior to commencing clinical trials in the respective countries, which may delay our clinical trials beyond our planned timeline. For example, in November 2022, the FDA placed the IND application to conduct a clinical trial evaluating VERVE-101 in the United States on hold and the IND remains on hold as of the date of this Annual Report on Form 10-K. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial, including with respect to VERVE-101, 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, delay the enrollment of our clinical trials or impose stricter approval conditions than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the European Union.

Commercialization of any product candidates we may develop will require preclinical and clinical development; regulatory and marketing approval in multiple jurisdictions, including by the FDA and the EMA; manufacturing supply, capacity and expertise; a commercial organization; and significant marketing efforts. The success of VERVE-101, VERVE-201 and any other product candidates we may identify and develop will depend on many factors, including the following:

- timely and successful completion of preclinical studies, including toxicology studies, biodistribution studies and minimally efficacious dose studies in animals, where applicable;
- effective INDs or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for any product candidates we may develop;
- successful enrollment and completion of clinical trials, including under the FDA's current Good Clinical Practices, or GCPs, current Good Laboratory Practices and any additional regulatory requirements from foreign regulatory authorities;
- positive results from our ongoing and future clinical trials that support a finding of safety and effectiveness and an acceptable risk-benefit profile in the intended populations;
- receipt of marketing approvals from applicable regulatory authorities;
- establishment of arrangements through our own facilities or with third-party manufacturers for clinical supply and, where applicable, commercial manufacturing capabilities;
- establishment, maintenance, defense and enforcement of patent, trademark, trade secret and other intellectual property protection or regulatory exclusivity for any product candidates we may develop;
- commercial launch of any product candidates we may develop, if approved, whether alone or in collaboration with others;
- acceptance of the benefits and use of our product candidates we may develop, including method of administration, if and when approved, by patients, the medical community and third-party payers;
- effective competition with other therapies;
- maintenance of a continued acceptable safety, tolerability and efficacy profile of any product candidates we may develop following approval; and
- establishment and maintenance of healthcare coverage and adequate reimbursement by payers.

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 any product candidates we may develop, which would materially harm our business. If we are unable to advance our product candidates through clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

Gene editing, including base editing, is a novel technology that is not yet clinically validated as being safe and efficacious for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics are unproven and may never lead to marketable products.

We are focused on developing medicines utilizing gene editing technology, which is new and largely unproven. The base editing technologies that we have licensed and that we are utilizing with VERVE-101 and VERVE -201 have not yet been evaluated in any completed clinical trial, nor are we aware of any clinical trials for safety or efficacy having been completed by third parties using our base editing or similar technologies. The scientific evidence to support the feasibility of developing product candidates based on gene editing technologies is both preliminary and limited. Successful development of our product candidates will require us to safely deliver a gene editor into target cells, optimize the efficiency and specificity of such product candidates and ensure the therapeutic selectivity of such product candidates. There can be no assurance that base editing technology, or other gene editing technology will lead to the development of genetic medicines or that we will be successful in solving any or all of these issues.

Our future success is highly dependent on the successful development of gene editing technologies, delivery technology methods and therapeutic applications of that technology. We may decide to alter or abandon our initial programs as new data become available and we gain experience in developing gene editing therapeutics. We cannot be sure that our technologies will yield satisfactory products that are safe and effective, scalable or profitable in our initial indications or any other indication we pursue. Adverse developments in the clinical development efforts of other gene editing technology companies could adversely affect our efforts or the perception of our product candidates by both investors and regulatory authorities.

Similarly, another new gene editing technology that has not been discovered yet may be developed by third parties and may be determined to be more attractive than base editing for the gene targets that we are pursuing with base editing technology.

We also are seeking to develop a novel gene editing development candidate as part of our collaboration with Vertex, including seeking to identify and engineer specific gene editing systems and delivery systems directed to a target of interest. We may seek to develop novel gene editing technology for future programs. We have not previously developed novel gene editing technology on our own and have in-licensed gene editing technology from third parties. We cannot be certain that we will be able to successfully develop novel gene editing systems for the target or for any other targets.

Moreover, we cannot be certain we will be able to obtain any necessary rights to develop other gene editing technologies. Although all of our founders who currently provide consulting and advisory services to us in the area of base editing technologies have assignment of inventions obligations to us with respect to the services they perform for us, these assignment of inventions obligations are subject to limitations and do not extend to their work in other fields or to the intellectual property arising from their employment with their respective academic and research institutions. To obtain intellectual property rights assigned by these founders to such institutions, we would need to enter into license agreements with such institutions, which may not be available on commercially reasonable terms or at all. Any of these factors could reduce or eliminate our commercial opportunity and could have a material adverse effect on our business, financial condition, results of operations and prospects.

Development activities in the field of gene editing are currently subject to a number of risks related to the ownership and use of certain intellectual property rights that are subject to patent interference proceedings in the United States and opposition proceedings in Europe. For additional information regarding the risks that may apply to our and our licensors' intellectual property rights, see the section entitled "—Risks related to our intellectual property" for more information.

Additionally, public perception and related media coverage relating to the adoption of new therapeutics or novel approaches to treatment, as well as ethical concerns related specifically to gene editing, may adversely influence the willingness of subjects to participate in clinical trials, or, if any therapeutic is approved, of physicians and patients to accept these novel and personalized treatments. Physicians, health care providers and third-party payors often are slow to adopt new products, technologies and treatment practices, particularly those that may also require additional upfront costs and training. Physicians may not be willing to undergo training to adopt these novel and potentially personalized therapies, may decide the particular therapy is too complex or potentially risky to adopt without appropriate training, and may choose not to administer the therapy. Further, due to health conditions, genetic profile or other reasons, certain patients may not be candidates for the therapies. In addition, responses by federal and state agencies, Congressional committees and foreign governments to negative public perception, ethical concerns or financial considerations may result in new legislation, regulations or medical standards that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be. Based on these and other factors, health care providers and payors may decide that the benefits of these new therapies do not or will not outweigh their costs.

The gene editing field is relatively new and is evolving rapidly. We are focusing our research and development efforts on gene editing using base editing technology, but other gene editing technologies may be discovered that provide significant advantages over base editing, which could materially harm our business.

To date, we have focused our efforts on gene editing technologies using base editing. Other companies have previously undertaken research and development of gene editing technologies using zinc finger nucleases,

engineered meganucleases and transcription activator-like effector nucleases, but to date none have obtained marketing approval for a product candidate. There can be no certainty that base editing technology will lead to the development of genetic medicines or that other gene editing technologies will not be considered better or more attractive for the development of medicines. For example, Feng Zhang's group at the Massachusetts Institute of Technology, or MIT, and Broad, and, separately, Samuel Sternberg's group at Columbia University announced the discovery of the use of transposons, or "jumping genes." Transposons can insert themselves into different places in the genome and can be programmed to carry specific DNA sequences to specific sites, without the need for making double-stranded breaks in DNA. Beam uses prime editing technology, which utilizes a CRISPR protein to target a mutation site in DNA and to nick a single strand of the target DNA. Guide RNA allows the CRISPR protein to recognize a DNA sequence that is complementary to the guide RNA and also carries a primer for reverse transcription and a replacement template. The reverse transcriptase copies the template sequence in the nicked site, installing the edit.

A number of alternative approaches are being developed by others, including, for example, Intellia Therapeutics, Inc., which has reported clinical data from a Phase 1b trial of NTLA-2001, a CRISPR/Cas9-based gene editing product candidate for the treatment of hereditary transthyretin amyloidosis with polyneuropathy and for the treatment of transthyretin (ATTR) amyloidosis with cardiomyopathy. Similarly, other new gene editing technologies that have not been discovered yet may be more attractive than base editing. Moreover, we cannot be certain we will be able to obtain rights to develop or use other gene editing technologies. Any of these factors could reduce or eliminate our commercial opportunity, and could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may not be successful in our efforts to identify and develop potential product candidates. If these efforts are unsuccessful, we may never become a commercial stage company or generate any revenues.

The success of our business depends primarily upon our ability to identify, develop and commercialize product candidates using gene editing technologies. We have only recently initiated our first clinical trial of VERVE-101 in New Zealand and the United Kingdom. Our research programs may fail to identify potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying additional potential product candidates, our potential product candidates may be shown to have harmful side effects in preclinical *in vitro* experiments or animal model studies, they may not show promising signals of therapeutic effect in such experiments or studies or they may have other characteristics that may make the product candidates impractical to manufacture, unmarketable or unlikely to receive marketing approval.

The COVID-19 pandemic may affect our ability to initiate and complete current or future preclinical studies, and clinical trials, disrupt regulatory activities or have other adverse effects on our business and operations. In addition, this pandemic has adversely impacted economies worldwide, which could result in adverse effects on our business, operations and prospects.

The COVID-19 pandemic has caused, and may continue to cause, many governments to implement measures to slow the spread of the pandemic through quarantines, travel restrictions, heightened border scrutiny and other measures. The pandemic and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen.

The future progression of the pandemic and its effects on our business and operations are uncertain. We and our contract manufacturing organizations, or CMOs, and contract research organizations, or CROs, have experienced a reduction in the capacity to undertake research-scale production and to execute some preclinical studies, and we have faced and may face disruptions that affect our ability to initiate and complete preclinical studies and clinical trials, and disruptions in procuring items that are essential for our research and development activities, including:

- raw materials and supplies used in the production and purification of messenger RNA, or mRNA, nucleic acids as well as lipids used in the production of lipid nanoparticles, or LNPs;
- raw materials and supplies used in the manufacture of any product candidates we may develop;
- laboratory supplies used in our preclinical studies and clinical trials; and
- animals that are used for preclinical testing for which there are shortages because of ongoing efforts to address components of the pandemic.

We and our CROs and CMOs may also face disruptions related to our ongoing and future IND-enabling studies and clinical trials arising from delays in preclinical studies, manufacturing disruptions, and the ability to obtain necessary institutional review board, or IRB, institutional biosafety committee, or IBC, or other necessary site approvals, as well as other delays at clinical trial sites.

The response to the COVID-19 pandemic may also redirect resources with respect to regulatory and intellectual property matters in a way that would adversely impact our ability to progress regulatory approvals and protect our intellectual property, for example by causing interruptions or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines. We have experienced delays with the FDA as a result of the COVID-19 pandemic. In addition, we may face impediments or delays to regulatory meetings and approvals due to measures intended to limit in-person interactions. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business, although for the reasons described above it has the potential to adversely affect our business, financial condition, results of operations and prospects.

Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

The risk of failure for each of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval. The time required to obtain approval from the FDA, EMA or other comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of regulatory authorities. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. We have only recently initiated a clinical trial for VERVE-101 in New Zealand and the United Kingdom and have not yet completed any clinical trials. Clinical trials may fail to demonstrate that our product candidates are safe for humans and effective for indicated uses. Even if initial clinical trials in any of our product candidates we may develop are successful, these product candidates we may develop may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through preclinical studies and initial clinical trials. There is a high failure rate for drugs and biologics proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical trials even after achieving promising results in earlier stage clinical trials. Furthermore, even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our planned INDs and other regulatory filings in the United States and abroad. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if the outcome of our preclinical testing and studies will ultimately support the further development of our current or future product candidates or whether regulatory authorities will accept our proposed clinical programs. As a result, we may not be able to submit an IND in the United States or comparable foreign applications to initiate clinical development on the timelines we expect, if at all, and the submission of these applications may not result in regulatory authorities allowing clinical trials to begin.

For example, in November 2022, the FDA placed our IND application to conduct a clinical trial evaluating VERVE-101 in the United States on hold. We received a clinical hold letter from the FDA in December 2022 that outlined the information required to resolve the clinical hold, including additional preclinical data relating to: (i) potency differences between human and non-human cells, (ii) risks of germline editing, and (iii) off-target analyses in non-hepatocyte cell types. The FDA also requested available clinical data from the ongoing heart-1 clinical trial. In addition, the FDA has requested that we modify the trial protocol in the United States to incorporate additional contraceptive measures and to increase the length of the staggering interval between dosing of participants.

Prior to initiating the trial in the United States, we will be required to resolve the hold on the IND application. We cannot be certain that the hold will be lifted on a timely basis, or at all, and we may not be able to initiate our clinical trial of VERVE-101 in the United States. Any delay in our ability, or our inability, to initiate our clinical trial of VERVE-101 in the United States because of the hold may delay our clinical development plans for VERVE-101, may require us to incur additional preclinical or clinical development costs and could impair our ability to ultimately obtain FDA approval for VERVE-101. Delays in the completion of any clinical trial of VERVE-101 could

increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue.

Furthermore, product candidates are subject to continued preclinical safety studies, which may be conducted concurrently with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any of our clinical trials will be conducted as planned or completed on schedule, or at all. A failure of one or more clinical trials can occur at any stage of testing, which may result from a multitude of factors, including, but not limited to, flaws in study design, dose selection issues, placebo effects, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits.

Preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Furthermore, the failure of any of our product candidates to demonstrate safety and efficacy in any clinical trial could negatively impact the perception of our other product candidates and/or cause the FDA, EMA or other regulatory authorities to require additional testing before approving any of our product candidates.

Our current and future product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA, EMA or other foreign regulatory authorities that a product candidate is safe, pure and potent or effective for its proposed indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA, EMA or other foreign regulatory authorities for approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA, EMA or other foreign regulatory authorities may disagree with our interpretation of data from clinical trials or preclinical studies;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a Biologics License Application, or BLA, to the FDA, or similar foreign submission to the EMA or other foreign regulatory authority, to obtain approval in the United States, the European Union or elsewhere;
- the FDA, EMA or other foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or other foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process as well as the unpredictability of clinical trial results may result in our failing to obtain regulatory approval to market any product candidate we develop, which would significantly harm our business, financial condition, results of operations and prospects.

The FDA, EMA and other comparable foreign regulatory authorities have substantial discretion in the approval process and determining when or whether regulatory approval will be obtained for any product candidate that we develop. Even if we believe the data collected from our ongoing or future clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA, EMA or any other comparable foreign regulatory authorities.

Even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Additionally, outside of the United States, regulatory authorities may not approve the price we intend to charge for our products. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

In response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and subsequently updated it on July 2, 2020, January 27, 2021, and August 30, 2021, to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study. In its most recent update to this guidance, FDA addresses questions received during the past year from clinical practitioners who are adapting their operations in a pandemic environment. These questions focused on, among other things, when to suspend, continue or initiate a trial and how to submit changes to protocols for INDs and handle remote site monitoring visits. There is no assurance that this guidance governing clinical studies during the pandemic will remain in effect or, even if it does, that it will help address the risks and challenges enumerated above. On January 30, 2023, the Biden Administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidance, including the clinical trial guidance and updates.

Accordingly, our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, slow down or halt our product candidate development and approval process and jeopardize our ability to seek and obtain the marketing approval required to commence product sales and generate revenue, which would cause the value of our company to decline and limit our ability to obtain additional financing if needed.

Accordingly, the COVID-19 pandemic may continue to significantly impact economies and financial markets worldwide, which could result in adverse effects on our business and operations, impact our ability to raise additional funds through public offerings and impact the volatility of our stock price and trading in our stock. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to adversely affect our business, financial condition, results of operations, and prospects.

The outcome of preclinical studies and earlier-stage clinical trials may not be predictive of future results or the success of later preclinical studies and clinical trials.

We have only recently initiated and begun conducting a clinical trial. As a result, our belief in the potential capabilities of our programs is based on research and preclinical studies. However, the results of preclinical studies may not be predictive of the results of later preclinical studies or clinical trials, and the results of any early-stage clinical trials may not be predictive of the results of later clinical trials. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. We have conducted several preclinical studies of our product candidates in non-human primates, but we cannot be certain that the results observed in such studies will translate into similar results in clinical trials of our product candidates in humans. Our ongoing or future clinical trials may not ultimately be successful or support further clinical development of any product candidates we may develop. There is a high failure rate for product candidates proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving encouraging results in earlier studies. Any such setbacks in our clinical development could materially harm our business and results of operations.

We may incur unexpected costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators, IRBs, or independent ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- regulators may decide that longer follow-up data are needed before they will consider our marketing application, which would delay our ability to obtain approval;
- regulators may decide the design of our clinical trials is flawed, for example if regulators do not agree with our chosen primary endpoints;
- regulators may decide to slow patient enrollment, resulting in delays to our ability to meet our timelines;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- preclinical testing may produce results based on which we may decide, or regulators may require us, to conduct additional preclinical studies before we proceed with certain clinical trials, limit the scope of our clinical trials, halt ongoing clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators, IRBs or ethics committees may require us to perform additional or unanticipated clinical trials to obtain approval or we may be subject to additional post-marketing testing requirements to maintain regulatory approval, such as a CVOT;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the trials; and
- regulators may withdraw their approval of a product or impose restrictions on its distribution, such as in the form of a risk evaluation and mitigation strategy, or REMS.

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are conducted or their ethics committees, by the data review committee or data safety monitoring board for such trial or by the FDA, EMA or other foreign regulatory authorities. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, EMA or other foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, including those relating to the class of products to which our product candidates belong.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling or a REMS that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Our development costs will also increase if we experience delays in preclinical studies or clinical trials or in obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. We may also determine to change the design or protocol of one or more of our clinical trials, including to add additional patients or arms, which could result in increased costs and expenses and/or delays. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Preclinical drug development is uncertain. Some or all of our preclinical programs may experience delays or may never advance to clinical trials, which would adversely affect our ability to obtain marketing approvals or commercialize these product candidates on a timely basis or at all, which would have an adverse effect on our business.

In order to obtain FDA approval to market a new biological product, we must demonstrate product purity (or product quality) as well as proof of safety and potency or efficacy in humans. To satisfy these requirements, we will have to conduct adequate and well-controlled clinical trials. Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support an IND in the United States. We cannot be certain of the timely completion or outcome of our preclinical testing and studies, and we cannot predict if the FDA will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of these product candidates. As a result, we cannot be sure that we will be able to submit INDs or similar applications for any preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing clinical trials to begin. For example, in November 2022, the FDA placed the IND application to conduct a clinical trial evaluating VERVE-101 in the United States on hold.

Conducting preclinical testing is a lengthy, time-consuming and expensive process. The length of time may vary substantially according to the type, complexity, novelty and intended use of the product candidate, and often can be several years or more per product candidate. Delays associated with product candidates for which we are conducting preclinical testing and studies ourselves may cause us to incur additional operating expenses. Moreover, we may be affected by delays associated with the preclinical testing and studies of certain product candidates conducted by our potential partners over which we have no control. The commencement and rate of completion of preclinical studies and clinical trials for a product candidate may be delayed by many factors, including, for example:

- inability to generate sufficient preclinical or other *in vivo* or *in vitro* data to support the initiation of clinical trials; and
- delays in reaching a consensus with regulatory agencies on study design.

Moreover, even if we do initiate clinical trials for other product candidates, our development efforts may not be successful, and clinical trials that we conduct or that third parties conduct on our behalf may not demonstrate product purity (or quality) as well as proof of safety and potency or efficacy necessary to obtain the requisite marketing approvals for any of our product candidates or product candidates employing our technology. Even if we obtain positive results from preclinical studies or initial clinical trials, we may not achieve the same success in future trials.

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.

Identifying and qualifying patients to participate in clinical trials for our product candidates is critical to our success. In 2022, we initiated our heart-1 clinical trial for VERVE-101 in New Zealand and the United Kingdom under country-specific protocols with various modifications to eligibility in each country. Successful and timely completion of clinical trials will require that we enroll a sufficient number of patients who remain in the trial until its conclusion. We may not be able to initiate or continue additional clinical trials for our product candidates 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 similar regulatory authorities outside of the United States. Given the large patient population for atherosclerotic cardiovascular disease, or ASCVD, if we expand clinical development of VERVE-101 or VERVE-201 for the treatment of patients with established ASCVD, the number of patients that may be required for clinical trials in order to obtain regulatory approval for that indication could be very high, and we may not be able to enroll a sufficient number of patients and as a result we may not be able to initiate or complete clinical trials of VERVE-101 for the treatment of patients with established ASCVD. Because of the small patient population for homozygous familial hypercholesterolemia, or HoFH, we may have difficulty enrolling patients and we may not be able to initiate or complete clinical trials for VERVE-201 for the treatment of HoFH.

Patient enrollment is affected by a variety of other factors, including:

- the prevalence and severity of the disease under investigation;
- the eligibility criteria for the trial in question;
- the perceived risks and benefits of the product candidate under trial;
- the requirements of the trial protocols, which for products targeting cardiovascular disease, or CVD, could include up to 15 years of long-term patient follow-up;
- the availability of existing treatments for the indications for which we are conducting clinical trials;
- the ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients;
- perceived negative public perception of gene editing;
- the conduct of clinical trials by competitors for product candidates that treat the same indications or address the same patient populations as our product candidates; and
- the cost to, or lack of adequate compensation for, prospective patients.

Other pharmaceutical and biotechnology companies have reported experiencing delays in enrollment in their ongoing clinical trials as a result of the COVID-19 pandemic, and we could also experience such delays. Our inability to locate and enroll a sufficient number of patients for our clinical trials would result in significant delays, could require us to abandon one or more clinical trials altogether and could delay or prevent our receipt of necessary regulatory approvals. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

Even if we are able to enroll a sufficient number of patients for our future clinical trials, we may have difficulty maintaining patients in our clinical trials. Many of the patients who end up receiving placebo may perceive that they are not receiving the product candidate being tested, and they may decide to withdraw from our clinical trials to pursue alternative therapies rather than continue the trial. If we have difficulty enrolling or maintaining a sufficient number of patients to conduct our clinical trials, we may need to delay, limit or terminate clinical trials, any of which would harm our business, financial condition, results of operations and prospects.

If any of the product candidates we may develop, or the delivery modes we rely on to administer them, cause serious adverse events, undesirable side effects or unexpected characteristics, such events, side effects or characteristics could delay or prevent regulatory approval of the product candidates, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

We only recently initiated our heart-1 clinical trial for VERVE-101. Moreover, there have been only a limited number of clinical trials involving the use of gene editing technologies and there are no completed clinical trials involving base editing technology similar to the gene editing technology we are using in VERVE-101. Furthermore, there has not been any gene editing product candidate that has received regulatory approval for use in humans. It is impossible to predict when or if any product candidates we may develop will prove safe in humans. There can be no assurance that gene editing technologies will not cause undesirable side effects, as

improper editing of a patient's DNA could lead to lymphoma, leukemia or other cancers or other aberrantly functioning cells.

A significant risk in any gene editing product candidate is that "off-target" edits may occur, which could cause serious adverse events, undesirable side effects or unexpected characteristics. We cannot be certain that off-target editing will not occur in any of our ongoing or future clinical studies, and the lack of observed side effects in preclinical studies does not guarantee that such side effects will not occur in human clinical studies. There is also the potential risk of delayed or late presentation of adverse events following exposure to gene editors due to the potential permanence of edits to DNA or due to other components of product candidates used to carry the genetic material. Further, because gene editing makes a permanent change, the therapy cannot be withdrawn, even after a side effect is observed.

We are using LNPs to deliver our gene editors to the liver. LNPs have recently been used to deliver mRNA in humans, including the COVID-19 vaccines developed by Pfizer Inc., or Pfizer, and BioNTech SE and by Moderna, Inc., and LNPs are being used to deliver mRNA for therapeutic use in clinical trials. LNPs have the potential to induce liver injury and/or initiate a systemic inflammatory response, either of which could potentially be fatal. While we aim to continue to optimize our LNPs, there can be no assurance that our LNPs will not have undesired effects. Our LNPs could contribute, in whole or in part, to one or more of the following: liver injury, immune reactions, infusion reactions, complement reactions, opsonization reactions, antibody reactions including IgA, IgM, IgE or IgG or some combination thereof, or reactions to the polyethylene glycol, or PEG, from some lipids or PEG otherwise associated with the LNP. Certain aspects of our investigational medicines may induce immune reactions from either the mRNA or the lipid as well as adverse reactions within liver pathways or degradation of the mRNA or the LNP, any of which could lead to significant adverse events in one or more of our ongoing or future clinical trials. Some of these types of adverse effects have been observed for other LNPs. There may be uncertainty as to the underlying cause of any such adverse event, which would make it difficult to accurately predict side effects in ongoing or future clinical trials and would result in significant delays in our programs.

Our GalNAc-LNPs, which we plan to use in VERVE-201, are a novel delivery mechanism for delivery of gene editors to the liver and have not yet been studied in humans.

If any product candidates we develop are associated with serious adverse events, undesirable side effects or unexpected characteristics, we may need to abandon their development or limit development to certain uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, any of which would have a material adverse effect on our business, financial condition, results of operations and prospects.

If in the future we are unable to demonstrate that any of the above adverse events were caused by factors other than our product candidate, the FDA, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, any product candidates we are able to develop for any or all targeted indications. They could also revoke a marketing authorization if a serious safety concern is identified in any post-marketing follow up studies. 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 we may develop, 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.

Adverse public perception of genetic medicines, and gene editing and base editing in particular, may negatively impact regulatory approval of, and/or demand for, our potential products.

Our programs involve editing the human genome. The clinical and commercial success of our product candidates will depend in part on public understanding and acceptance of the use of gene editing therapy 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 product candidates may not gain the acceptance of the public or the medical community. 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 addition, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns.

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 product candidates we may develop. Adverse events in our preclinical studies or clinical trials or those of our licensors, partners or 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. Use of gene editing technology by a third party or government to develop biological agents or products that threaten U.S. national security could similarly result in such negative impacts to us.

Interim and preliminary results from our clinical trials that we announce or publish from time to time may change as more participant data become available and are subject to audit and verification procedures, which could result in material changes in the final data.

From time to time, we may publish or report interim or preliminary results from our clinical trials. Interim results from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as participant enrollment continues and more participant data become available. We also make assumptions, estimations, calculations, and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully evaluate all data. Preliminary, interim or top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary or interim data we previously published. As a result, preliminary, interim or top-line data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could be material and could significantly harm our reputation and business prospects and may cause the trading price of our common stock to fluctuate significantly.

Genetic medicines are complex and difficult to manufacture. We could experience delays in satisfying regulatory authorities or production problems that result in delays in our development programs, limit the supply of our product candidates we may develop, or otherwise harm our business.

Any product candidates we may develop will likely require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as the product candidates we intend to develop generally cannot be fully characterized. As a result, assays of the finished product candidate may not be sufficient to ensure that the product candidate will perform in the intended manner. 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 or potentially delay progression of our potential IND filings. If we successfully develop product candidates, we may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other comparable applicable foreign standards or specifications with consistent and acceptable production yields and costs. In addition, the product candidates we may develop will require complicated delivery modalities, such as LNPs, which will introduce additional complexities in the manufacturing process.

In addition, the FDA, the EMA and other 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 regulatory authorities may require that we not distribute a lot until the 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 or product recalls could cause us to delay clinical trials or product launches, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We also may encounter problems hiring and retaining the experienced scientific, quality control and manufacturing personnel needed to manage our manufacturing process, which could result in delays in our production or difficulties in maintaining compliance with applicable regulatory requirements.

Given the nature of biologics manufacturing, there is a risk of contamination during manufacturing. Any contamination could materially harm our ability to produce product candidates on schedule and could harm our results of operations and cause reputational damage. Some of the raw materials that we anticipate will be required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of any product candidates we may develop could

adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially harm our development timelines and our business, financial condition, results of operations and prospects.

Any problems in our manufacturing process or the facilities with which we contract 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 third-party manufacturing process or facilities also could restrict our ability to ensure sufficient clinical material for any clinical trials we may be conducting or are planning to conduct and meet market demand for any product candidates we develop and commercialize.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the drug could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If one or more of our product candidates receives regulatory approval, and we, or others, later discover that they are less effective than previously believed, or cause undesirable side effects, a number of potentially significant negative consequences could result, including:

- withdrawal or limitation by regulatory authorities of approvals of such product;
- seizure of the product by regulatory authorities;
- recall of the product;
- restrictions on the marketing of the product or the manufacturing process for any component thereof;
- requirement by regulatory authorities of additional warnings on the label, such as a “black box” warning or contraindication;
- requirement that we implement a REMS or create a medication guide outlining the risks of such side effects for distribution to patients;
- commitment to expensive post-marketing studies as a prerequisite of approval by regulatory authorities of such product;
- the product may become less competitive;
- initiation of regulatory investigations and government enforcement actions;
- initiation of legal action against us to hold us liable for harm caused to patients; and
- harm to our reputation and resulting harm to physician or patient acceptance of our products.

Any of these events could prevent us from achieving or maintaining market acceptance of a particular product candidate, if approved, and could significantly harm our business, financial condition, and results of operations.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Failure to allocate resources or capitalize on strategies in a successful manner will have an adverse impact on our business, financial condition and results of operations.

We are conducting a clinical trial, and plan to conduct additional clinical trials at sites outside the United States. The FDA may not accept data from trials conducted in such locations, and the conduct of trials outside the United States could subject us to additional delays and expense.

We are conducting and plan to conduct one or more additional clinical trials with one or more trial sites that are located outside the United States, including our ongoing Phase 1b trial of VERVE-101 at trial sites in New Zealand and the United Kingdom. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and be performed by qualified investigators in accordance with ethical principles. The FDA must be able to validate the data from the trial through an onsite inspection, if necessary. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, whether the FDA accepts the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and could delay or permanently halt our development of the applicable product candidates.

In addition, conducting clinical trials outside the United States could have a significant adverse impact on us. Risks inherent in conducting international clinical trials include:

- clinical practice patterns and standards of care that vary widely among countries;
- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange fluctuations; and
- diminished protection of intellectual property in some countries.

Risks related to our dependence on third parties

We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our product manufacturing, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to many of these items, including CMOs for the manufacturing of any product candidates we test in preclinical or clinical development, as well as CROs for the conduct of our animal testing and research. Any of these third parties may terminate their engagements with us at any time or may face supply chain shortages or otherwise be unable to secure the requisite resources, such as animals used in our preclinical testing, to support our planned development activities. If we need to modify our development plans or enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols.

Although we intend to design the clinical trials for any product candidates we may develop, CROs will conduct some or 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 ongoing and 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 and other third parties do not perform preclinical studies and ongoing 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 any product candidates we may develop 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 and other third parties, we could be required to repeat, extend the duration of or increase the size of any preclinical studies or clinical trials we conduct and this could significantly delay commercialization and require greater expenditures.

If third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support future IND submissions and approval of any product candidates we may develop.

Manufacturing biologic products is complex and subject to product loss for a variety of reasons. We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of VERVE-101 and our other product candidates for preclinical and clinical testing, as well as for commercial manufacture if any of our product candidates receive marketing approval. We also rely on these third parties for packaging, labeling, sterilization, storage, distribution and other production logistics. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

We or our third-party manufacturers may encounter shortages in the raw materials or active pharmaceutical ingredients, or API, necessary to produce our product candidates in the quantities needed for our clinical trials or, if our product candidates are approved, in sufficient quantities for commercialization or to meet an increase in demand, as a result of capacity constraints or delays or disruptions in the market for the raw materials or API, including shortages caused by the purchase of such raw materials or API by our competitors or others. The failure of us or our third-party manufacturers to obtain the raw materials or API necessary to manufacture sufficient quantities of our product candidates may have a material adverse effect on our business.

Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP. Our third-party manufacturers are subject to inspection and approval by regulatory authorities before we can commence the manufacture and sale of any of our product candidates, and thereafter subject to ongoing inspection from time to time. Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in regulatory actions, such as the issuance of FDA Form 483 notices of observations, warning letters or sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Manufacturing biologic products, such as VERVE-101, is complex, especially in large quantities. Biologic products must be made consistently and in compliance with a clearly defined manufacturing process. Accordingly, it is essential to be able to validate and control the manufacturing process to assure that it is reproducible. The manufacture of biologics is extremely susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, vendor or operator error, inconsistency in yields, variability in product characteristics and difficulties in scaling the product process. We have not yet scaled up the manufacturing process for any of our product candidates for potential commercialization. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. If microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination, which could harm our results of operations and cause potential reputational damage. Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. As a result, we may not obtain access to these facilities on a priority basis or at all. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance nor do we have any agreements with third-party manufacturers for long-term commercial supply. If any of our future contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement or be unable to reach agreement with an alternative manufacturer.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

If any third-party manufacturer of our product candidates is unable to increase the scale of its production of our product candidates, and/or increase the product yield of its manufacturing, then our costs to manufacture the product candidate may increase and commercialization may be delayed.

In order to produce sufficient quantities to meet the demand for clinical trials and, if approved, subsequent commercialization of any current or future product candidates that we may develop, our third-party manufacturers will be required to increase their production and optimize their manufacturing processes while maintaining the quality of the product. The transition to larger scale production could prove difficult. In addition, if our third-party manufacturers are not able to optimize their manufacturing processes to increase the product yield for our product candidates, or if they are unable to produce increased amounts of our product candidates while maintaining the quality of the product, then we may not be able to meet the demands of our ongoing or future clinical trials or market demands, which could decrease our ability to generate profits and have a material adverse impact on our business and results of operation.

We have entered into collaborations, and may enter into additional collaborations, with third parties for the research, development, manufacture and commercialization of programs or product candidates. If these collaborations are not successful, our business could be adversely affected.

As part of our strategy, we have entered into collaborations and intend to seek to enter into additional collaborations with third parties for one or more of our programs or product candidates. For example, in April 2019, we entered into the Beam Agreement to exclusively license certain of Beam's base editing, gene editing and delivery technology against certain cardiovascular targets for use in our product candidates, which agreement was amended and restated in July 2022; in October 2020, we entered into the Acuitas Agreement to license from Acuitas its LNP delivery technology that we are using in VERVE-101; in October 2021 we entered into the Novartis Agreement to license from Novartis certain lipid technology that we are using in VERVE-201; and in July 2022, we entered into the Vertex Agreement for a four-year worldwide research collaboration focused on developing *in vivo* gene editing candidates toward an undisclosed target for the treatment of a single liver disease. Our likely collaborators for any other collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We have under the Beam Agreement, and we may have under any other arrangements that we may enter into with any third parties, limited control over the amount and timing of resources that collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these

arrangements may depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations that we enter into may not be successful, and any success will depend heavily on the efforts and activities of such collaborators. Collaborations pose a number of risks, including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development of our product candidates or may elect not to continue or renew development programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew commercialization programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;
- collaborators may delay preclinical studies and clinical trials, provide insufficient funding for a preclinical study or clinical trial program, stop a preclinical study or clinical trial or abandon a product candidate, repeat or conduct new preclinical studies or clinical trials or require a new formulation of a product candidate for preclinical or clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates on a discretionary basis;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates and products 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;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over intellectual property or proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly obtain, maintain, enforce, defend or protect our intellectual property or proprietary rights or may use our proprietary information in such a way as to potentially lead to disputes or legal proceedings that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. If any current or future collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this "Risk Factors" section also apply to the activities of our collaborators.

Collaboration agreements may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. For example, upon execution of the Beam Agreement, we issued 276,075 shares of our common stock to Beam and in connection with the execution of the Vertex Agreement, we completed a private placement with Vertex pursuant to which we issued 1,519,756 shares of our common stock to Vertex. In addition, under the Cas9 License Agreement, we issued 138,037 shares of our common stock to Broad and Harvard. Broad and Harvard also had anti-dilution rights, pursuant to which we issued Broad and Harvard an additional 309,278 shares of our common stock in the aggregate following the completion of preferred stock financings. We also issued 878,098 additional shares of common stock to Broad and Harvard upon the closing of our IPO pursuant to the Cas9 License Agreement. We are also obligated to pay to Harvard and Broad tiered success payments in the event our average market capitalization exceeds specified thresholds ascending from a high nine-digit dollar amount to $10.0 billion, or sale of our company for consideration in excess of those thresholds. In the event of a change of control of our company or a sale of our company, we are required to pay any related success payment in cash within a specified period following such event. Otherwise, the success payments may be settled at our option in either cash or shares of our common stock, or a combination of cash and shares of our common stock. In September 2021, we notified Harvard and Broad that our average market capitalization exceeded three specified thresholds as of a relevant measurement date and aggregate success payments of approximately $6.3 million became payable under the Cas9 License Agreement, which we settled in cash in November 2021.

We could face significant competition in seeking appropriate collaborators, and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement 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 several factors. If we license rights to any product candidates we or our collaborators may develop, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. 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.

If we are not able to establish or maintain collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans and our business could be adversely affected.

We face significant competition in attracting appropriate collaborators, and a number of more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we consider attractive. These established companies may have a competitive advantage over us due to their size, financial 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. Whether we reach a definitive agreement for a collaboration 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 the FDA, EMA or other regulatory authorities, 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 products, 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, the terms of any existing collaboration agreements, and industry and market conditions generally. The collaborator may also have the opportunity to collaborate on other product candidates or technologies for similar indications and will have to evaluate whether such a collaboration could be more attractive than the one with us for our product candidate.

We may also be restricted under existing or future license agreements from entering into agreements on certain terms with potential collaborators.

Collaborations are complex and time-consuming to negotiate, document and execute. In addition, consolidation among large pharmaceutical and biotechnology companies has reduced the number of potential future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms or at all. If we are unable to do so, 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 fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market.

We depend on single-source suppliers for some of the components and materials used in our product candidates.

We depend on single-source suppliers for some of the components and materials used in our product candidates. We cannot ensure that these suppliers or service providers will remain in business, have sufficient capacity or supply to meet our needs or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of single-source suppliers of raw materials, components, key processes and finished goods exposes us to several risks, including disruptions in supply, price increases or late deliveries. There are, in general, relatively few alternative sources of supply for substitute components. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components, materials and processes could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any single-source supplier or service provider could lead to supply delays or interruptions, which would damage our business, financial condition, results of operations and prospects.

If we have to switch to a replacement supplier, the manufacture and delivery of any product candidates we may develop could be interrupted for an extended period, which could adversely affect our business. Establishing additional or replacement suppliers, if required, may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. While we seek to maintain adequate inventory of the single source components and materials used in our products, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand for our product candidates.

Risks related to our intellectual property

If we or our licensors are unable to obtain, maintain, defend and enforce patent rights that cover our gene editing technology and product candidates or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected.

Our success depends in large part on our ability to obtain, maintain, defend, and enforce protection of the intellectual property we may own solely and jointly with others or may license from others, particularly patents, in the United States and other countries with respect to proprietary technology and product candidates we develop. It is difficult and costly to protect our gene editing technologies and product candidates, and we may not be able to ensure their protection. Our ability to stop unauthorized third parties from making, using, selling, offering to sell, importing or otherwise commercializing our product candidates we may develop, or operatively similar products, is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates that are important to our business and by in-licensing intellectual property related to our

technologies and product candidates. If we are unable to obtain or maintain patent protection with respect to any proprietary technology or product candidate, our business, financial condition, results of operations and prospects could be materially harmed. Failure to obtain protection including patent protection, may be a result of specific legal and factual circumstances that may preclude the availability of protection for our product candidates in the United States or any given country. For example, inadequate, faulty or erroneous patent prosecution may result in diminution, loss or unavailability of patent rights that adequately cover our products. Patent disclosures and claims that are intended to cover our product candidates that are sufficient or allowable in one country may not be sufficient or allowable in another country. The requirements for filing a patent application in the United States may not be sufficient to support a patent filing in a country or region outside the United States.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, defend or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce and defend the patents, covering technology that we license from third parties. Therefore, these in-licensed patents and applications may not be prepared, filed, prosecuted, maintained, defended and enforced in a manner consistent with the best interests of our business.

The patent position of pharmaceutical and biotechnology companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The field of gene editing especially has been the subject of extensive patenting activity and litigation. In addition, the scope of patent protection outside of the United States is uncertain and laws of foreign countries may not protect our rights to the same extent as the laws of the United States or vice versa. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Further, no earlier than the second quarter of 2023, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court, or the UPC. This will be a significant change in European patent practice. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation.

With respect to both owned and in-licensed patent rights, 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. Further, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates.

In addition, 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 published at all. Therefore, neither we nor our licensors can know with certainty whether either we or our licensors were the first to make the inventions claimed in the patents and patent applications we own or in-license now or in the future, or that either we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our owned and in-licensed patent rights are highly uncertain. Moreover, our owned and in-licensed pending and future patent applications may not result in patents being issued which protect our technology and product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents and our ability to obtain, protect, maintain, defend and enforce our patent rights, narrow the scope of our patent protection and, more generally, could affect the value or narrow the scope of our patent rights.

Moreover, we or our licensors may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. If the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Additionally, 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 our owned and in-licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. 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 abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us. 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. Furthermore, our competitors may be able to circumvent our owned or in-licensed patents by developing similar or alternative technologies or products in a non-infringing manner. As a result, our owned and in-licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing technology and products similar or identical to any of our technology and product candidates.

Our rights to develop and commercialize our gene editing technology and product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We depend on intellectual property licensed from third parties, and our licensors may not always act in our best interest. If we fail to comply with our obligations under our intellectual property licenses, if the licenses are terminated, or if disputes regarding these licenses arise, we could lose significant rights that are important to our business.

We have licensed and are dependent on certain patent rights and proprietary technology from third parties that are important or necessary to the development of our gene editing technology and product candidates. For example, we are a party to the Beam Agreement, the Cas9 License Agreement, the Acuitas Agreement, the Novartis Agreement, and other license agreements, pursuant to which we in-license and have acquired key patents and patent applications for our gene editing technology, LNP technology and product candidates. These license agreements impose various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with these obligations, our licensors may have the right to terminate our license, in which event we would not be able to develop or market our gene editing technology or product candidates covered by the intellectual property licensed under these agreements.

These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our gene editing technology and product candidates in the future. Some licenses and acquired patents granted to us are expressly subject to certain preexisting rights held by the licensor or certain third parties. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in certain territories or fields. If we determine that rights to such excluded fields are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to continue developing, manufacturing or marketing our product candidates. We may not be able to obtain such a license on an exclusive basis, on commercially reasonable terms, or at all, which could prevent us from commercializing our product candidates or allow our competitors or others the chance to access technology that is important to our business.

In addition, pursuant to the Cas9 License Agreement, under certain specific circumstances, Harvard and Broad may grant a license to the patents that are the subject of such license agreements to a third party in the same field as such patents are licensed to us. Such third party may then have full rights that are the subject of the Cas9 License Agreement, which could impact our competitive position and enable a third party to commercialize products similar to our potential future product candidates and technology. Any grant of rights to a third party in this scenario would narrow the scope of our exclusive rights to the patents and patent applications we have in-licensed from Harvard and Broad.

We do not have complete control in the preparation, filing, prosecution, maintenance, enforcement and defense of patents and patent applications covering the technology that we license or have acquired from third parties. It is possible that our licensors' enforcement of patents against infringers or defense of such patents against challenges of validity or claims of enforceability may be less vigorous than if we had conducted them ourselves, or may not be conducted in accordance with our best interests. We cannot be certain that these patents and patent applications will be prepared, filed, prosecuted, maintained, enforced and defended in a manner consistent with

the best interests of our business. If our licensors fail to prosecute, maintain, enforce and defend such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, our right to develop and commercialize any of our product candidates we may develop that are the subject of such licensed rights could be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

Our licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents we in-licensed. If other third parties have ownership rights to our in-licensed patents, the license granted to us in jurisdictions where the consent of a co-owner is necessary to grant such a license may not be valid and such co-owners may be able to license such patents to our competitors, and our competitors could market competing products and technology. In addition, our rights to our in-licensed patents and patent applications are dependent, in part, on inter-institutional or other operating agreements between the joint owners of such in-licensed patents and patent applications. If one or more of such joint owners breaches such inter-institutional or operating agreements, our rights to such in-licensed patents and patent applications may be adversely affected. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

Furthermore, inventions contained within some of our in-licensed patents and patent applications were made using U.S. government funding. We rely on our licensors to ensure compliance with applicable obligations arising from such funding, such as timely reporting, an obligation associated with our in-licensed patents and patent applications. The failure of our licensors to meet their obligations may lead to a loss of rights or the unenforceability of relevant patents. For example, the U.S. government could have certain rights in such in-licensed patents, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. If the U.S. government decides to exercise these rights, it is not required to engage us as its contractor in connection with doing so. The U.S. government's rights may also permit it to disclose the funded inventions and technology to third parties and to exercise march-in rights to use or allow third parties to use the technology we have licensed that was developed using U.S. government funding. The U.S. government may also exercise its march-in rights if it determines that action is necessary because we or our licensors failed to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, our rights in such in-licensed U.S. government-funded inventions may be subject to certain requirements to manufacture product candidates embodying such inventions in the United States. Any of the foregoing could harm our business, financial condition, results of operations and prospects significantly.

In the event any of our third-party licensors determine that, in spite of our efforts, we have materially breached a license agreement or have failed to meet certain obligations thereunder, it may elect to terminate the applicable license agreement or, in some cases, one or more license(s) under the applicable license agreement, and such termination would result in us no longer having the ability to develop and commercialize product candidates and technology covered by that license agreement or license. In the event of such termination of a third-party in-license, or if the underlying patents under a third-party in-license fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

Our owned and in-licensed patents and patent applications and other intellectual property may be subject to priority or inventorship disputes, interferences and similar proceedings. If we or our licensors are unsuccessful in any of these proceedings, we may be required to obtain licenses from third parties, which may not be available on commercially reasonable terms or at all, or to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop, which could have a material adverse impact on our business.

Certain of the U.S. patents and one U.S. patent application to which we hold an option are co-owned by Broad and MIT, and in some cases co-owned by Broad, MIT and Harvard, which we refer to together as the Boston Licensing Parties, and were involved in U.S. Interference No. 106,048 with one U.S. patent application co-owned by the University of California, the University of Vienna, and Emmanuelle Charpentier, which we refer to together as CVC. On September 10, 2018, the Court of Appeals for the Federal Circuit, or the CAFC, affirmed the Patent Trial and Appeal Board of the USPTO's, or PTAB's, holding that there was no interference-in-fact. An interference is a proceeding within the USPTO to determine priority of invention of the subject matter of patent claims filed by different parties.

On June 24, 2019, the PTAB declared a second interference (U.S. Interference No. 106,115) between 14 U.S. patent applications that are co-owned by CVC, and 13 U.S. patents and one U.S. patent application (that are co-owned by the Boston Licensing Parties). In the declared interference, CVC has been designated as the junior party and the Boston Licensing Parties have been designated as the senior party. On February 28, 2022, the PTAB held that the Boston Licensing Parties had priority over CVC with respect to Count 1 of the interference: a single RNA CRISPR-Cas9 system that functions in eukaryotic cells. As a result, CVC's patent applications involved in this interference were deemed unpatentable. In September 2022, the CVC appealed the PTAB's decision at the CAFC and the appeal is ongoing.

On December 20, 2020, the PTAB declared an interference (U.S. Interference No. 106,126) between one U.S. patent application owned by Toolgen, Inc. and 14 U.S. patents and two U.S. patent applications that are co-owned by the Boston Licensing Parties. In the declared interference, Boston Licensing Parties have been designated as the junior party and Toolgen, Inc. has been designated as the senior party.
The PTAB has currently suspended these subsequent interference proceedings with Toolgen and Sigma-Aldrich, pending the CAFC's decision of the appeal between the CVC and the Boston Licensing Parties over the outcome of the second interference.

On June 21, 2021, the PTAB declared an interference (U.S. Interference No. 106,133) between one U.S. patent application owned by Sigma-Aldrich Co., LLC and 14 U.S. patents and two U.S. patent applications that are co-owned by the Boston Licensing Parties. In the declared interference, Boston Licensing Parties have been designated as the junior party and Sigma-Aldrich Co., LLC has been designated as the senior party.

The PTAB has currently suspended these subsequent interference proceedings with Toolgen and Sigma-Aldrich, pending the CAFC's decision of the appeal between the CVC and the Boston Licensing Parties over the outcome of the second interference.

As a result of the declaration of interference, an adversarial proceeding in the USPTO before the PTAB has been initiated, which is declared to ultimately determine priority, specifically and which party was first to invent the claimed subject matter. An interference is typically divided into two phases. The first phase is referred to as the motions or preliminary motions phase while the second is referred to as the priority phase. In the first phase, each party may raise issues including but not limited to those relating to the patentability of a party's claims based on prior art, written description, and enablement. A party also may seek an earlier priority benefit or may challenge whether the declaration of interference was proper in the first place. Priority, or a determination of who first invented the commonly claimed invention, is determined in the second phase of an interference. Although we cannot predict with any certainty how long each phase will actually take, each phase may take approximately a year or longer before a decision is made by the PTAB. It is possible for motions filed in the preliminary motions phase to be dispositive of the interference proceeding, such that the second priority phase is not reached.

There can be no assurance that the current appeal or these pending U.S. interference proceedings will be resolved in favor of the Boston Licensing Parties. If the appeal in the second interference favors CVC, or the 106,126, or 106,133 interference resolves in favor of Toolgen, Inc., or Sigma-Aldrich Co., LLC, respectively, or if the Boston Licensing Parties' patents and patent application are narrowed, invalidated, or held unenforceable, we will lose the ability to license the optioned patents and patent application and our ability to commercialize our product candidates may be adversely affected if we cannot obtain a license to relevant third-party patents that cover our product candidates. 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 nonexclusive, 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. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our gene editing technology or product candidates or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

We or our licensors may also be subject to claims that former employees, collaborators, or other third parties have an interest in our owned patent applications or in-licensed patents or patent applications or other intellectual property as an inventor or co-inventor. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patent applications, such co-owners rights may be subject, or in the future subject, to assignment or license to other third parties, including our competitors. In addition, we may need the cooperation of any such co-owners to enforce any patents that issue from such patent applications against third parties, and such cooperation may not be provided to us.

If we or our licensors are unsuccessful in any interference proceedings or other priority, validity (including any patent oppositions) or inventorship disputes to which we or they are subject, we may lose valuable intellectual

property rights through the loss of one or more of our owned, licensed or optioned patents, or such patent claims may be narrowed, invalidated or held unenforceable, or through loss of exclusive ownership of or the exclusive right to use our owned or in-licensed patents. In the event of loss of patent rights as a result of any of these disputes, we may be required to obtain and maintain licenses from third parties, including parties involved in any such interference proceedings or other priority or inventorship disputes. 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 may need to cease the development, manufacture and commercialization of one or more of the product candidates we may develop. 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 product candidates. Even if we or our licensors are successful in an interference proceeding, other similar priority disputes, or inventorship or ownership disputes, it could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could result in a material adverse effect on our business, financial condition, results of operations or prospects.

If we fail to comply with our obligations in our intellectual property licenses arrangements with third parties, or otherwise experience disruptions to our business relationships with our licensors, we could lose intellectual property rights that are important to our business.

We are party to agreements, and we may enter into additional arrangements, with third parties that may impose diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. We have existing agreements, pursuant to which we are obligated to pay royalties on net product sales of product candidates or related technologies to the extent they are covered by the agreements. If we fail to comply with such obligations under current or future agreements, our counterparties may have the right to terminate these agreements or require us to grant them certain rights. Such an occurrence could materially adversely affect the value of any product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, which would have a material adverse effect on our business, financial condition, results of operations and prospects. While we still face all of the risks described herein with respect to those agreements, we cannot prevent third parties from also accessing those technologies. In addition, our licenses may place restrictions on our future business opportunities.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the agreement and other interpretation related issues;
- the extent to which our technology and processes infringe on 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;
- our diligence obligations under the 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 are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, 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 technology and product candidates, which could have a material adverse effect on our business, financial conditions, results of operations and prospects.

Our current or future licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the intellectual property or intellectual property rights we in-license. If other third parties have ownership rights to intellectual property or intellectual property rights we in-license, they may be able to license such intellectual property or intellectual property rights to our competitors, and our competitors could market competing products and technology. This could have a

material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

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 product candidates and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products and technologies identical to ours. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

If we are unable to obtain licenses from third parties on commercially reasonable terms or fail to comply with our obligations under such agreements, our business could be harmed.

We currently have rights to intellectual property, through licenses from third parties, to identify and develop product candidates, and we expect to seek to expand our product candidate pipeline in part by in-licensing the rights to key technologies. Although we have succeeded in licensing technologies from third-party licensors including Harvard, Broad, Beam, Acuitas, and Novartis in the past, we cannot assure our stockholders that we will be able to in-license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all.

Various third parties practice in competitive technology areas and may have issued patents or patent applications that will issue as patents in the future, which could impede or preclude our ability to commercialize our product candidates. For any third-party patents that could be relevant to our product candidates, we rely in part on the "safe harbor" or research exemption under 35 U.S.C. § 271(e)(1), which exempts from patent infringement activities related to pursuing FDA approval for a drug product. However, while U.S. patent law provides such a "safe harbor" to our clinical product candidates under this provision, that exemption expires when an IND or BLA is submitted. Given the uncertainty of clinical trials, we cannot be certain of the timing of their completion and it is possible that we may submit a BLA for one of our product candidates at a time when one or more relevant third-party patents is in force.

It may therefore be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales or an obligation on our part to pay royalties and/or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

Furthermore, there has been extensive patenting activity in the field of gene editing, and pharmaceutical companies, biotechnology companies, and academic institutions are competing with us or are expected to compete with us in the field of gene editing technology and filing patent applications potentially relevant to our business, and there may be third-party patent applications that, if issued, may allow the third party to circumvent our patent rights. Because of the large number of patents issued and patent applications filed in our field, these and other third parties could allege they have patent rights encompassing our product candidates, technologies or methods. In order to market our product candidates, we may find it necessary or prudent to obtain licenses from such third-party intellectual property holders. 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 and gene editing technology we may develop. We may also require licenses from third parties for certain gene editing technologies including certain delivery and gene editing compositions and methods that we are evaluating, or may in the future evaluate, for use with product candidates we may develop. In addition, some of our owned patent applications and in-licensed patents and patent applications may be determined to be co-owned with third parties. With respect to any patents co-owned with third parties, we may require licenses to such co-owners' interest to such patents. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us.

Additionally, we may collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Even if we hold such an option, we may be unable to negotiate a license from the institution within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program.

In addition, the licensing or acquisition of third-party intellectual property rights is a highly competitive area, and a number of more established companies are also pursuing strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These 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. 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 or product candidate, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If we are unable to obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology and product candidates, which could harm our business, financial condition, results of operations and prospects significantly.

Additionally, if we fail to comply with our obligations under license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market, or may be forced to cease developing, manufacturing or marketing, any product that is covered by these agreements or may face other penalties under such agreements. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements, or restrictions on our ability to freely assign or sublicense our rights under such agreements when it is in the interest of our business to do so, may result in our having to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology or impede, or delay or prohibit the further development or commercialization of one or more product candidates that rely on such agreements.

The intellectual property landscape around genome editing technology, including base editing, is highly dynamic, and third parties may initiate legal proceedings alleging that we are infringing, misappropriating, or otherwise violating their intellectual property rights, the outcome of which would be uncertain and may prevent, delay or otherwise interfere with our product discovery and development efforts.

Our commercial success depends upon our ability and the ability of our collaborators to research, develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. The field of genome editing, especially in the area of base editing technology, is still in its infancy, and no such product candidates 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 evolving and in flux, and it may remain uncertain for the coming years. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights as well as administrative proceedings for challenging patents, including interference, derivation, *inter partes* review, post grant review, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. 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. We may be 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 gene editing platform technology and any product candidates we may develop, including interference proceedings, post-grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions such as oppositions before the

European Patent Office. Numerous U.S. and foreign issued patents and pending patent applications that are owned by third parties exist in the fields in which we are developing our product candidates and they may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit.

As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our gene editing technology and product candidates may give rise to claims of infringement of the patent rights of others. Moreover, it is not always clear to industry participants, including us, which patents cover various types of therapies, products or their methods of use or manufacture. We are aware of certain third-party patent applications that, if issued, may be construed to cover our gene editing technology and product candidates. There may also be third-party patents of which we are currently unaware with claims to technologies, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. 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 infringes upon these patents.

It is possible that we have failed to identify relevant third-party patents or applications that our product candidates and programs may infringe. Because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of any product candidates we may develop or our technology, and we may not be aware of such patents. Furthermore, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States may remain confidential until a patent issues. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to any product candidates we may develop and our technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, any product candidates we may develop or the use of any product candidates we may develop.

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. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize our product candidates or any other of our 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.

Numerous third-party U.S. and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates. Our product candidates make use of CRISPR-based gene editing technology, which is a field that is highly active for patent filings. The extensive patent filings related to CRISPR and Cas make it difficult for us to assess the full extent of relevant patents and pending applications that may cover our gene editing technology and product candidates and their use or manufacture. There may be third-party patents or patent applications, including patents held or controlled by our competitors with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our gene editing technology and product candidates.

If we are found to infringe, misappropriate or otherwise violate a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidates and 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 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 monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right indemnify our customers

or collaborators. A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. The terms of individual patents depend upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest non-provisional filing date in the applicable country. However, the actual protection afforded by a patent varies from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including biosimilars. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Our product candidates may face competition from biosimilars approved through an abbreviated regulatory pathway.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-approved reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first approved by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first approved. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing 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 the other company's product. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty.

We believe that any of our product candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to Congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of our marketing exclusivity for any product candidates we may develop, our business may be materially harmed.

In the United States, the patent term of a patent that covers an FDA-approved drug may be eligible for limited patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under clinical development and regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, and only one patent applicable to and that covers an approved drug may be extended. Similar provisions are available in Europe, such as supplementary protection certificates,

and certain other non-United States jurisdictions to extend the term of a patent that covers an approved drug. While, in the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. We may not be granted patent term extension either in the United States or in any foreign country 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 term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. If we are unable to obtain any patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following the expiration of our patent rights, and our business, financial condition, results of operations and prospects could be materially harmed.

It is possible that we will not obtain patent term extension under the Hatch-Waxman Act for a U.S. patent covering any of our product candidates that we may identify even where that patent is eligible for patent term extension, or if we obtain such an extension, it may be for a shorter period than we had sought.

Changes to patent laws in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our gene editing platform technology and product candidates.

As is the case with other biotech and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain.

Changes in either the patent laws or interpretation of patent laws in the United States, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our owned and in-licensed patent applications and the maintenance, enforcement or defense of our owned and in-licensed issued patents. The Leahy-Smith Act includes a number of significant changes to United States patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could 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 have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Past U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future. For example, in the case, *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.,* the U.S. Supreme Court held that claims to certain DNA molecules are not patentable. More recently, in *Amgen Inc. v. Sanofi*, the Federal Circuit held that claims with functional language may pose high hurdles in fulfilling the enablement requirement for claims with broad

functional language. We cannot predict how this and future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patents. Any similar adverse changes in the patent laws of other jurisdictions could also have a material adverse effect on our business, financial condition, results of operations and prospects.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court.

If we or one of our licensing partners initiates legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate 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, written description or non-enablement. In addition, patent validity challenges may, under certain circumstances, be based upon non-statutory obviousness-type double patenting, which, if successful, could result in a finding that the claims are invalid for obviousness-type double patenting or the loss of patent term, including a patent term adjustment granted by the USPTO, if a terminal disclaimer is filed to obviate a finding of obviousness-type double patenting. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product candidates. 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 of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

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, and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. 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 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. 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.

Intellectual property litigation or other legal proceedings relating to intellectual property could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments 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 stock. 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 conduct such litigation or proceedings adequately. 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 and may also have an advantage in such proceedings due to their more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of intellectual property litigation or other proceedings could compromise our ability to compete in the marketplace.

Obtaining and maintaining 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, renewal and annuity fees and various other government fees on any issued patent and pending patent application must be paid to the USPTO and foreign patent agencies in several stages or annually over the lifetime of our owned and in-licensed patents and patent applications. 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. In certain circumstances, we may rely on our licensing partners to pay these fees to, or comply with the procedural and documentary rules of, the relevant patent agency. With respect to our patents, we rely on outside firms and outside counsel to remind us of the due dates and to make payment after we instruct them to do so. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of 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 such an event, potential competitors might be able to enter the market with similar or identical products or technology. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, it would have a material adverse effect on our business, financial condition, results of operations and prospects.

We have limited foreign intellectual property rights and may not be able to protect our intellectual property and proprietary rights throughout the world.

We have limited intellectual property rights outside the United States. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, and even where such protection is nominally available, judicial and governmental enforcement of such intellectual property rights may be lacking. 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 obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection or licenses but enforcement is not as strong as that in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. 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. In addition, certain jurisdictions do not protect to the same extent or at all inventions that constitute new methods of treatment.

Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions 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 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 are 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.

Furthermore, geo-political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future

licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors. For example, the United States and foreign government actions related to Russia's invasion of Ukraine may limit or prevent filing, prosecution and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our licensed patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees that have citizenship or nationality in, are registered in, or have a predominantly primary place of business or profit-making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

We may be subject to claims by third parties asserting that our employees, consultants or contractors have wrongfully used or disclosed confidential information of third parties, or we have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, consultants and contractors were previously employed at universities or other pharmaceutical or biotechnology companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the 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 develops intellectual property that we regard as our own. Our intellectual property assignment agreements with them may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims 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 conditions, results of operations and prospects.

If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive business position and prospects. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

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 our 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 information, to maintain our competitive position. We seek to protect our 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, CMOs, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants, but we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology. 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. Detecting the disclosure or misappropriation of a trade secret and 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 to contractual measures, we try to protect the confidential nature of our proprietary information through other appropriate precautions, such as physical and technological security measures. However, trade secrets and

know-how can be difficult to protect. These measures may not, for example, in the case of misappropriation of a trade secret by an employee or third party with authorized access, provide adequate protection for our proprietary information. Our security measures may not prevent an employee or consultant from misappropriating our trade secrets and providing them to a competitor, and any recourse we might take against this type of misconduct may not provide an adequate remedy to protect our interests fully. In addition, trade secrets may be independently developed by others in a manner that could prevent us from receiving legal recourse. If any of our confidential or proprietary information, such as our trade secrets, were to be disclosed or misappropriated, or if any of that information was independently developed by a competitor, our competitive position could be harmed.

In addition, some courts inside and outside of the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, 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 our trademarks and trade names 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.

Any registered trademarks or trade names may be challenged, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, 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.

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:

- any product candidates we may develop will eventually become commercially available in generic or biosimilar product forms;
- others may be able to make gene editing products that are similar to ours but that are not covered by the claims of the patents that we own;
- 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 applications 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 in-licensed intellectual property rights;
- it is possible that our pending owned and in-licensed patent applications or those we may own or in-license in the future will not lead to issued patents;
- it is possible that there are prior public disclosures that could invalidate our owned or in-licensed patents, or parts of our owned or in-licensed patents;
- it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our product candidates or technology similar to ours;

- it is possible that our owned or in-licensed patents or patent applications omit individual(s) that should be listed as inventor(s) or include individual(s) that should not be listed as inventor(s), which may cause these patents or patents issuing from these patent applications to be held invalid or unenforceable;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- the laws of foreign countries may not protect our proprietary rights or the proprietary rights of license partners or current or future collaborators to the same extent as the laws of the United States;
- the inventors of our owned or in-licensed patents or patent applications may become involved with competitors, develop products or processes that design around our patents, or become hostile to us or the patents or patent applications on which they are named as inventors;
- 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 have engaged in scientific collaborations in the past and will continue to do so in the future and our collaborators may develop adjacent or competing products that are outside the scope of our patent rights;
- we cannot ensure that any of our patents, or any of our pending patent applications, if issued, or those of our licensors, will include claims having a scope sufficient to protect our product candidates;
- we cannot ensure that any patents issued to us or our licensors will provide a basis for an exclusive market for our commercially viable product candidates or will provide us with any competitive advantages;
- we cannot ensure that our commercial activities or product candidates will not infringe upon the patents of others;
- we cannot ensure that we will be able to successfully commercialize our product candidates on a substantial scale, if approved, before our relevant patents that we own or license expire;
- 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.

Risks related to commercialization

Even if any of our current or future product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for any of such product candidates, if approved, may be smaller than we estimate.

If any of our current or future product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, current CVD treatments such as statins, ezetimibe, bempedoic acid, lomitapide, mipomersen and icosapent ethyl are well-established in the medical community, and physicians may continue to rely on these treatments.

Even if VERVE-101, VERVE-201 or any other product candidate we develop meets its safety and efficacy endpoints in clinical trials, we cannot be certain that success in clinical trials will ensure success as a commercial product. For example, in September 2022, AstraZeneca and Ionis Pharmaceuticals, Inc. determined not to advance an antisense oligonucleotide PCSK9 inhibitor dosed once monthly via subcutaneous administration into Phase 3 clinical development for the treatment of hypercholesterolemia following a Phase 2b clinical trial that met its primary endpoint and achieved a statistically significant 62.3% reduction in low density lipoprotein cholesterol, or LDL-C, after 28 weeks compared to
placebo on the basis that the results did not meet AstraZeneca's target product profile criteria to invest in a broad Phase 3 development program.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If our current or future product candidates do not achieve

an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our current or future product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages of such product candidates compared to the advantages and relative risks of alternative treatments;
- the effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar biosimilar treatments;
- our ability to offer our products, if approved, for sale at competitive prices;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement, and patients' willingness to pay out of pocket for required co-payments or in the absence of third-party coverage or adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products, if approved, together with other medications.

Our assessment of the potential market opportunity for our current or future product candidates is based on industry and market data that we obtained from industry publications, research, surveys and studies conducted by third parties and our analysis of these data, research, surveys and studies. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. Our estimates of the potential market opportunities for our product candidates include a number of key assumptions based on our industry knowledge, industry publications and third-party research, surveys and studies, which may be based on a small sample size and fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of our assumptions or estimates, or these publications, research, surveys or studies prove to be inaccurate, then the actual market for any of our product candidates may be smaller than we expect, and as a result our revenues from product sales may be limited and it may be more difficult for us to achieve or maintain profitability.

We face substantial competition, which may result in others discovering, developing or commercializing products before us or more successfully than we do.

The development and commercialization of new drug or biologic products is highly competitive. It is particularly competitive with respect to new products for CVD, for which the standard of care is well-established. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many of the disease indications for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

There are several approved products for LDL-C lowering or cardiovascular risk reduction, such as statins, ezetimibe, bempedoic acid, lomitapide, mipomersen and icosapent ethyl. There are several approved products that target PCSK9 protein as a mechanism to lower LDL-C and reduce the risk of ASCVD. Evolocumab, which is a monoclonal antibody, or mAb, marketed as Repatha® by Amgen Inc., is approved by the FDA for the treatment of patients with heterozygous familial hypercholesterolemia, or HeFH, patients with HoFH and patients with

ASCVD. Alirocumab, which is a mAb marketed as PRALUENT® by both Sanofi and Regeneron Pharmaceuticals, Inc., or Regeneron, is approved by the FDA for the treatment of patients with ASCVD and for the treatment of patients with primary hyperlipidemia, including HeFH. The approved mAb treatments act through extracellular inhibition of the PCSK9 protein. Inclisiran, which is a small interfering RNA, or siRNA, marketed as Leqvio®by Novartis, is approved in the United States for the treatment of patients with clinical ASCVD or HeFH who require additional lowering of LDL-C and in Europe for the treatment of patients with hypercholesterolemia, including HeFH, or mixed dyslipidemia. Inclisiran acts by inhibiting the synthesis of PCSK9 within liver cells, which is distinct from extracellular protein inhibition. We are also aware of three orally administered small molecule product candidates that target the PCSK9 protein as a mechanism to lower LDL-C and reduce the risk of ASCVD in various stages of clinical development. These include MK-0616 from Merck & Co., Inc, which was studied in a recently completed Phase 2b trial of adult patients with hypercholesterolemia with a plan to release results in the first quarter of 2023; an oral small molecule from Serometrix LLC in-licensed by Esperion Therapeutics, which disclosed plans in 2022 to submit an IND in late 2024 or early 2025; and AZD0780, acquired by AstraZeneca from Dogma Therapeutics, which is being evaluated in an ongoing Phase 1 clinical trial.

We are aware of two other gene editing programs targeting the PCSK9 gene in preclinical development. Precision Biosciences, Inc., or Precision, has published preclinical data showing long-term stable reduction of PCSK9 and LDL-C levels in non-human primates following *in vivo* gene editing of the PCSK9 gene using its gene editing platform. In September 2021, Precision entered into a collaboration with iECURE under which iECURE plans to advance Precision's PCSK9 directed nuclease product candidate into Phase 1 clinical trials for the treatment of FH in 2022. In January 2023, Precision announced that it had decided to cease pursuit of this program with iECURE as a partner, with plans to provide additional guidance on whether and when this medicine will advance into clinical testing in the future. Additionally, in 2022, CRISPR Therapeutics, or CRISPR, announced CTX330, its research stage *in vivo* gene editing program targeting PCSK9.

Evinacumab, which is a mAb targeting ANGPTL3 protein that is marketed by Regeneron is approved by the FDA for the treatment of patients with HoFH and has additionally been evaluated in Phase 2 studies of patients with refractory hypercholesterolemia and either ASCVD or HeFH, and severe hypertriglyceridemia. We are aware of several product candidates in clinical development that target ANGPTL3 as a mechanism to lower LDL-C and reduce the risk of ASCVD, including ARO-ANG3, a siRNA targeting ANGPTL3 being evaluated by Arrowhead Pharmaceuticals in Phase 2 clinical trials of patients with HoFH and patients with mixed dyslipidemia. In 2022, Arrowhead announced plans to initiate pivotal Phase 3 studies of ARO-ANG3 in patients with HoFH and patients with HeFH in the second half of 2023. In addition, Eli Lilly and Company is evaluating a siRNA targeting ANGPTL3 protein in a Phase 2 study in adults with mixed dyslipidemia, and in 2022, CRISPR announced CTX310, its gene editing program targeting ANGPTL3, which is in IND-enabling studies with plans for initial patient dosing in 2023.

Several investigational medicines designed to reduce lipoprotein(a), or LP(a), are currently in development. These include pelecarsen, an antisense oligonucleotide licensed by Novartis from Ionis Pharmaceuticals in 2019, which is being evaluated in the Phase 3 Lp(a) HORIZON cardiovascular outcomes study in patients with high Lp(a) and cardiovascular disease, with topline results expected in 2025. Olpasiran is an investigational siRNA medicine targeting LPA licensed by Amgen from Arrowhead Pharmaceuticals, which was recently shown to lower LP(a) concentrations in patients with established ASCVD and high Lp(a) concentrations. The potential for Olpasiran to reduce cardiovascular events in patients with existing ASCVD and high Lp(a) will be evaluated in the OCEAN(a) study, which was initiated in 2022 with plans for study completion in 2026. In addition, SLN360 is an investigational siRNA medicine being developed by Silence Therapeutics plc that is being evaluated in an ongoing Phase 2 study of patients with high Lp(a) concentrations and high risk for ASCVD events, and, in 2022, CRISPR announced CTX320, its research stage *in vivo* gene editing program targeting *LPA*.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than 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. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium to competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future 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 and biotechnology industry 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.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our current and future product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience as a company with the commercialization of products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

In the future, we expect to build a sales and marketing infrastructure to market some of our product candidates in the United States, if and when they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. 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. These efforts 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 products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales, marketing, coverage or reimbursement, customer service, medical affairs and other support personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the inability of reimbursement professionals to negotiate arrangements for coverage, formulary access, reimbursement and other acceptance by payors;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;
- the lack of complementary products 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 are unable to establish our own sales, marketing and distribution capabilities and we enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are acceptable 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 products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We currently rely, and expect to continue to rely, on CMOs to manufacture our product candidates. If we are unable to enter into such arrangements as expected or if such organizations do not meet our supply requirements, development and/or commercialization of our product candidates may be delayed.

We currently rely, and expect to continue to rely on third parties to manufacture clinical supplies of our product candidates and commercial supplies of our products, if and when approved for marketing by applicable regulatory authorities, as well as for packaging, sterilization, storage, distribution and other production logistics. If we are unable to enter into such arrangements on the terms or timeline we expect, development and/or commercialization of our product candidates may be delayed. If these third parties do not successfully carry out

their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, if there are disagreements between us and such parties or if such parties are unable to expand capacities to support commercialization of any of our product candidates for which we obtain marketing approval, we may not be able to fulfill, or may be delayed in producing sufficient product candidates to meet, our supply requirements. These facilities may also be affected by catastrophic events, including pandemics, including the ongoing COVID-19 pandemic, terrorist attacks, wars or other armed conflicts, geopolitical tensions, such as the ongoing conflict between Russia and Ukraine, natural disasters, such as floods or fire, or such facilities could face manufacturing issues, such as contamination or regulatory concerns following a regulatory inspection of such facility. In such instances, we may need to locate an appropriate replacement third-party facility and establish a contractual relationship, which may not be readily available or on acceptable terms, which would cause additional delay and increased expense, including as a result of additional required FDA approvals, and may have a material adverse effect on our business.

Our third-party manufacturers will be subject to inspection and approval by the FDA before we can commence the manufacture and sale of any of our product candidates, and thereafter subject to FDA inspection from time to time. Failure by our third-party manufacturers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidates may result in regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses.

We or our third-party manufacturers may also encounter shortages in the raw materials or API necessary to produce our product candidates in the quantities needed for our clinical trials or, if our product candidates are approved, in sufficient quantities for commercialization or to meet an increase in demand, as a result of capacity constraints or delays or disruptions in the market for the raw materials or API, including shortages caused by the purchase of such raw materials or API by our competitors or others. The failure of us or our third-party manufacturers to obtain the raw materials or API necessary to manufacture sufficient quantities of our product candidates may have a material adverse effect on our business.

Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party coverage or reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign 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 our product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a 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.

In the United States, there is no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor

supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford our product candidates, if approved. Our ability to achieve acceptable levels of coverage and reimbursement for our product candidates, if approved, by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize, our product candidates. Assuming we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require patient out-of-pocket costs that patients find unacceptably high.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and 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. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, 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 drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs 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 drugs 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 adequate reimbursement rates from both government-funded and private payors for any approved products that we 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.

There can be no assurance that our product candidates, even if they are approved for sale in the United States or in other countries, will be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payors, or that coverage and an adequate level of reimbursement will be available or that third-party payors' reimbursement policies will not adversely affect our ability to sell our product candidates profitably.

Our future growth depends, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties that, if they materialize, could harm our business.

Our future profitability will depend, in part, on our ability to commercialize our product candidates in markets outside of the United States. If we commercialize our product candidates in foreign markets, we will be subject to additional risks and uncertainties, including:

- economic weakness, including inflation, or political instability in particular economies and markets;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, many of which vary between countries;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- tariffs and trade barriers, as well as other governmental controls and trade restrictions;
- other trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or foreign governments;

- longer accounts receivable collection times;
- longer lead times for shipping;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is common;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries, and related prevalence of biosimilar alternatives to therapeutics;
- foreign currency exchange rate fluctuations and currency controls;
- differing foreign reimbursement landscapes;
- uncertain and potentially inadequate reimbursement of our products; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

If risks related to any of these uncertainties materializes, it could have a material adverse effect on our business.

Clinical trial and product liability lawsuits against us could divert our resources and could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We will face an inherent risk of clinical trial and product liability exposure related to the testing of our product candidates in human clinical trials, and we will face an even greater risk if we commercially sell any products that we may develop. While we currently have no products that have been approved for commercial sale, the ongoing, planned and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

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

We currently do not hold any clinical trial liability insurance coverage. We may need to obtain insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to obtain and maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Risks related to regulatory approval and other legal compliance matters

Gene editing is novel and the regulatory landscape that will govern any product candidates we may develop is uncertain and may change. As a result, we cannot predict the time and cost of obtaining regulatory approval, if we receive it at all, for any product candidates we may develop.

The regulatory requirements that will govern any novel gene editing product candidates we develop are not entirely clear and may change. Within the broader genetic medicines field, we are aware of a limited number of gene therapy products that have received marketing authorization from the FDA and the EMA. Even with respect to more established products that fit into the categories of gene therapies or cell therapies, the regulatory

landscape is still developing. Regulatory requirements governing gene therapy products and cell therapy products have changed frequently and will likely continue to change in the future. Moreover, there is substantial, and sometimes uncoordinated, overlap in those responsible for regulation of existing gene therapy products and cell therapy products. For example, in the United States, the FDA has established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical trials may also be subject to review and oversight by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at the institution participating in the clinical trial. Although the FDA decides whether individual gene therapy protocols may proceed, the review process and determinations of other reviewing bodies can impede or delay the initiation of a clinical trial, even if the FDA has reviewed the trial and approved its initiation.

The same applies in the European Union. In the European Union, the development and evaluation of a gene therapy medicinal product must be considered in the context of the relevant EU guidelines. The EMA may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines. Additionally, for advanced therapy medicinal products, a marketing application authorization undergoes review by the EMA's Committee for Advanced Therapies, or CAT, in addition to review by the Committee for Medicinal Products for Human Use, or CHMP. As a result, the procedures and standards applied to gene therapy products and cell therapy products may be applied to any product candidates we may develop, but that remains uncertain at this point.

Adverse developments in post-marketing experience or in clinical trials conducted by others of gene therapy products, cell therapy products, or products developed through the application of a base editing or other gene editing technology may cause the FDA, the EMA, and other regulatory bodies to revise the requirements for development or approval of any product candidates we may develop or limit the use of products utilizing base editing technologies, either of which could materially harm our business. In addition, 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 potential products. The regulatory approval process for novel product candidates such as the product candidates we may develop can be more expensive and take longer than for other, better known, or more extensively studied pharmaceutical or other product candidates. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of products utilizing base editing technology in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays, or other impediments to our research programs or the commercialization of resulting products.

The regulatory review committees and advisory groups described above and the new 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 these treatment candidates, or lead to significant post-approval limitations or restrictions. As we advance our research programs and develop future product candidates, we will be required to consult with these regulatory and advisory groups and to comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of any product candidates we identify and develop.

Because we are developing product candidates in the field of genetic medicines, a field that includes gene therapy and gene editing, in which there is little clinical experience, there is increased risk that the FDA, the EMA, or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results and that these results may be difficult to analyze.

During the regulatory review process, we will need to identify success criteria and endpoints such that the FDA, the EMA, or other regulatory authorities will be able to determine the clinical efficacy and safety profile of any product candidates we may develop. As we are seeking to identify and develop product candidates to treat diseases in which there is no clinical experience using a gene editing approach, there is heightened risk that the FDA, the EMA, or other regulatory authorities may not consider the clinical trial endpoints that we propose to provide clinically meaningful results (reflecting a tangible benefit to patients). In addition, the resulting clinical data and results may be difficult to analyze. Even if the FDA does find our success criteria to be sufficiently validated and clinically meaningful, we may not achieve the pre-specified endpoints to a degree of statistical significance. Further, even if we do achieve the pre-specified criteria, we may produce results that are unpredictable or inconsistent with the results of the non-primary endpoints or other relevant data. The FDA also weighs the benefits of a product against its risks, and the FDA may view the efficacy results in the context of safety as not

being supportive of regulatory approval. Other regulatory authorities in the European Union and other countries may make similar comments with respect to these endpoints and data. Any product candidates we may develop will be based on a novel technology that makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval. No gene editing therapeutic product has been approved in the United States or in Europe.

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 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 develop, and our ability to generate revenue will be materially impaired.

Any product candidates we 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 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. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction. We have no experience as a company in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity and potency. 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. 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.

The process of obtaining marketing approvals, both in the United States and abroad, 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 and the specific disease or condition to be treated. Of the large number of products in development, only a small percentage successfully complete the FDA or foreign regulatory approval processes and are commercialized. Even if any product candidates we may develop demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. 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 is 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 develop, the commercial prospects for those product candidates may be harmed and our ability to generate revenues will be materially impaired.

Obtaining and maintaining marketing approval or commercialization of our product candidates in the United States does not mean that we will be successful in obtaining marketing approval of our product candidates in other jurisdictions. Failure to obtain marketing approval in foreign jurisdictions would prevent any product candidates we develop from being marketed in such jurisdictions, which, in turn, would materially impair our ability to generate revenue.

In order to market and sell any product candidates we may develop in the European Union and many other foreign jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying local regulatory requirements. The approval procedure varies among countries and can involve

additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any jurisdiction, which would materially impair our ability to generate revenue.

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020 and European Union rules and regulations ceased to apply to the United Kingdom starting on January 1, 2021. The Medicines and Healthcare products Regulatory Agency, or the MHRA, is now the sole decision maker for marketing authorizations of pharmaceutical products in the United Kingdom, except for Northern Ireland. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the United Kingdom the body of European Union law governing medicinal products that pre-existed before the United Kingdom's withdrawal from the European Union.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, the consequences of Brexit and the impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom remains unclear. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm our business. As a result of Brexit, we expect we will need to submit a separate application to the MHRA for marketing approval in the United Kingdom, in addition to any planned marketing authorization applications for the EMA.

We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States.

We may seek certain designations for our product candidates, including Fast Track, Breakthrough Therapy, Regenerative Medicine Advanced Therapy and Priority Review designations in the United States, Innovative Licensing and Access Pathway designation in the United Kingdom, and PRIME Designation in the European Union, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process.

If a product candidate is intended for the treatment of a serious or life-threatening condition and the product candidate demonstrates the potential to address unmet medical need for this condition, the sponsor may apply to the FDA for Fast Track designation. 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.

In addition, an applicant may seek designation of its product as a breakthrough therapy, which is a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs and biologics 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.

Additionally, a product is eligible for Regenerative Medicine Advanced Therapy, or RMAT, designation if it is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of an RMAT designation are similar to a breakthrough therapy designation, and include early interactions with the FDA to expedite development and review, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Further, if the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product 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 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.

We may seek these and other designations for our product candidates. The FDA has broad discretion with respect to whether or not to grant these designations 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 Fast Track, breakthrough therapy, or RMAT designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. As a result, while we may seek and receive these designations for our product candidates, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw these designations if it believes that the designation is no longer supported by data from our clinical development program.

In the European Union, we may seek PRIME designation for some of our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the European Union or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the European Union and the applicant intends to apply for an initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims. The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME also encourages an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

We may equally pursue some of the post-Brexit UK MHRA procedures to prioritize access to new medicines that will benefit patients, such as a 150-day assessment, a rolling review procedure and an innovative licensing and access pathway, or ILAP. ILAP aims to accelerate the time to market and to facilitate patient access to medicines, including new chemical entities, biological medicines, new indications and repurposed medicines. We received our innovation passport, which is the point of entry into the ILAP, from the MHRA on February 14, 2023. Product developers that benefit from ILAP will be provided with advice on clinical trial design to ensure optimal data generation for both regulatory approval and health technology appraisal.

We may not be able to obtain orphan drug exclusivity for any product candidates we may develop, and even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by the EMA in the European Union. Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing

application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the agency must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the United States. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In particular, the concept of what constitutes the "same drug" for purposes of orphan drug exclusivity remains in flux in the context of gene therapies, and the FDA has issued recent final guidance suggesting that it would not consider two genetic medicine products to be different drugs solely based on minor differences in the transgenes or vectors. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition.

In 2017, the Congress passed the FDA Reauthorization Act of 2017, or the FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017, but have not yet been approved or licensed by FDA.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved. Depending on what changes the FDA or Congress may make to its orphan drug regulations and policies, our business could be adversely impacted.

Negative public opinion of gene editing and increased regulatory scrutiny of gene editing and genetic research may adversely impact public perception of our future product candidates.

Our potential therapeutic products involve introducing genetic material into patients' cells. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene editing and gene regulation for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene editing and gene regulation are unsafe, unethical or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. 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.

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products once approved. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. The risk of cancer remains a concern for gene editing and we cannot

assure that it will not occur in any of our planned or future clinical trials. If any such adverse events occur, commercialization of our product candidates or further advancement of our clinical trials could be halted or delayed, which would have a negative impact on our business and operations.

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, cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. For example, 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 FDA typically advises that patients treated with genetic medicine undergo follow-up observations for potential adverse events for up to a 15-year period. 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. 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.

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. 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 obtain marketing approval could be subject to restrictions or withdrawal from the market, and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we 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 medicines to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. Although physicians may prescribe products for uses not described in the product's labeling, known as off-label uses, in their professional medical judgment, the FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we market our products, if approved, in a manner inconsistent with their approved labeling, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the Department of Justice, or DOJ. Violation of the Federal Food, Product, 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 September 2021, the FDA published final regulations that describe the types of evidence that the FDA will consider in determining the intended use of a drug or biologic.

In addition, later discovery of previously unknown problems with our product candidates, manufacturers, or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers, or manufacturing processes;
- restrictions on the labeling or marketing of a medicine;
- restrictions on the distribution or use of a medicine;
- requirements to conduct post-marketing clinical trials;

- receipt of warning or untitled letters;
- withdrawal of the medicines from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of medicines;
- fines, restitution, or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- suspension of any ongoing clinical trials;
- refusal to permit the import or export of our medicines;
- product seizure; and
- injunctions or the imposition of civil or criminal penalties.

Any government investigation of alleged violations of law 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 inhibit our ability to commercialize any product candidates we develop and adversely affect our business, financial condition, results of operations, and prospects.

Inadequate funding for the FDA, the SEC and other government agencies, including from government shut downs, or other disruptions to these agencies' operations, could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory and policy changes. Average review times at the agency have fluctuated in recent years as a result. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. In addition, government funding of the Securities and Exchange Commission, or the SEC, and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Separately, in response to the COVID-19 pandemic, a number of companies announced in 2021 receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Following a period of false starts and temporary suspensions due to the omicron variant, the FDA resumed domestic inspections in February 2022 and indicated that it would conduct foreign inspections beginning in April 2022 on a prioritized basis However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

Any relationships we may have with customers, healthcare providers and professionals, and third-party payors, among others, will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we are able to obtain marketing approval. Any arrangements we have with healthcare providers, third-party payors and customers will subject us to broadly applicable fraud and abuse and other healthcare laws and regulations. The laws and regulations may constrain the business or financial arrangements and relationships through which we conduct clinical research, market, sell and distribute any products for which we obtain marketing approval. These include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, 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 under federal and state healthcare programs such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the federal False Claims Act, which can be enforced through civil whistleblower or qui tam actions, and civil monetary penalty laws impose civil and criminal penalties against individuals or entities for knowingly presenting or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid or other government payers that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme or artifice to defraud any healthcare benefit program 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, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as further amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, which imposes certain requirements, including mandatory contractual terms, on covered entities subject to the rule, such as health plans, healthcare clearinghouses and certain healthcare providers, as well as their respective business associates and their subcontractors that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security, and transmission of such individually identifiable health information;
- the federal transparency requirements under the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services, or HHS, information related to payments and other transfers of value to physicians, as defined by such law, and teaching hospitals and other covered recipients and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations, and, as of January 2022, requires applicable manufacturers to report information regarding payments and other transfers of value provided during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants, and certified nurse midwives; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers, and certain state laws that 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 drug manufacturers to report information related to drug pricing and payments to physicians and other healthcare providers or marketing expenditures and state and local laws that require the registration of sales representatives; and state and foreign laws governing 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.

Efforts to ensure that any business arrangements we have with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm, and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. Further, if any of the physicians or other healthcare 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.

Current and future legislation may increase the difficulty and cost for us and any collaborators to obtain marketing approval and commercialize our product candidates and affect the prices we, or they, may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell or commercialize any product candidate for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products.

In March 2010, President Obama signed into law the PPACA. In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, 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 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to two percent per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. Pursuant to the CARES Act and subsequent legislation, these Medicare sequester reductions were suspended through the end of June 2022 but the full 2% cut resumed thereafter on July 1, 2022. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, the Tax Act repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. However, on June 17, 2021, the U.S. Supreme Court dismissed the case and sustained the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The former Trump presidential administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those orders and

issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Executive Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents. This Executive Order also directs the HHS to create a special enrollment period for the Health Insurance Marketplace in response to the COVID-19 pandemic.

We expect that these healthcare reform measures, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue 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 or commercialize product candidates. It is also possible that additional governmental action will be taken in response to the COVID-19 pandemic.

The prices of prescription pharmaceuticals in the United States and foreign jurisdictions is subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized 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 creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2032 by the Inflation Reduction Act.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new

discounting program (beginning in 2025). The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least nine years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

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, health care organizations 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.

In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the United States and the European Union, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the United States, European Union and United Kingdom. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached certain contracts with our business partners. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agent-the California Privacy Protection Agency-whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah and Connecticut, already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three stats will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Similar to the laws in the United States, there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or EEA, and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross-border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

The GDPR places restrictions on the cross-border transfer of personal data from the European Union to countries that have not been found by the European Commission to offer adequate data protection legislation, such as the United States. There are ongoing concerns about the ability of companies to transfer personal data from the European Union to other countries. In July 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU-U.S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA

to the United States. The CJEU's decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. While we were not self-certified under the EU-U.S. Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EEA to the United States generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the European Union.

Following the withdrawal of the United Kingdom from the European Union, the United Kingdom's Data Protection Act 2018 applies to the processing of personal data that takes place in the United Kingdom and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the United Kingdom and the European Union have determined, through separate "adequacy" decisions, that data transfers between the two jurisdictions are in compliance with the UK's Data Protection Act and the GDPR, respectively. Any changes or updates to these adequacy decisions have the potential to impact our business.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the United States regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business, financial condition, results of operations or prospects.

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, vendors, consultants and partners, and, for our clinical trials, our principal investigators and CROs. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union 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 abroad, 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. 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 significant fines or other sanctions.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates outside of the United States and require us to develop and implement costly compliance programs.

We are subject to numerous laws and regulations in each jurisdiction outside the United States in which we operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the DOJ. The SEC is involved with enforcement of the books and records provisions of the FCPA.

Compliance with the FCPA and other anti-corruption laws potentially applicable to our business is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the compliance with the FCPA and other anti-corruption laws presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

We are also subject to other laws and regulations governing our international operations, including applicable export control laws, economic sanctions on countries and persons, and customs requirements. In addition, various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the United States has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and drug candidates outside of the United States, which could limit our growth potential and increase our development costs.

There is no assurance that we will be completely effective in ensuring our compliance with the FCPA and other applicable anti-corruption, export, sanctions, and customs laws. The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violations of these laws, including the FCPA, can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

If we or any third-party manufacturer we engage now or in the future fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs or liabilities that could have a material adverse effect on our business.

We and third-party manufacturers we engage now are, and any third-party manufacturer we may engage in the future will be, 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 generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury

from these materials. In the event of contamination or injury resulting from our use 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.

Although we maintain general liability insurance as well as workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

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 commercialization efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Further, with respect to the operations of our current and any future third-party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products. In addition, our supply chain may be adversely impacted if any of our third-party contract manufacturers become subject to injunctions or other sanctions as a result of their non-compliance with environmental, health and safety laws and regulations.

Risks related to employee matters and managing growth

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, financial, operational and other business expertise of Sekar Kathiresan, M.D., our chief executive officer, Andrew Ashe, J.D., our president, chief operating officer, and general counsel, Allison Dorval, our chief financial officer, and Andrew Bellinger, M.D., Ph.D., our chief scientific officer and chief medical officer, as well as the other principal members of our management, scientific and clinical teams. 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. Recruiting and retaining qualified scientific, clinical, manufacturing, accounting, legal and sales and marketing personnel will also be critical to our success.

The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain marketing approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. 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. Our success also depends on implementing and maintaining internal controls and the accuracy and timeliness of our financial reporting. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As our development progresses, we expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical, regulatory affairs, manufacturing and quality control and, if any of our product candidates receive marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional

qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Future acquisitions or strategic alliances could disrupt our business and harm our financial condition and results of operations.

We may acquire additional businesses, technologies or assets, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products or product candidates resulting from a strategic alliance or acquisition that may delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure our stockholders that, following any such acquisition, we will achieve the expected synergies to justify the transaction. The risks we face in connection with acquisitions include:

- diversion of management time and focus from operating our business to addressing acquisition integration challenges;
- coordination of research and development efforts;
- retention of key employees from the acquired company;
- changes in relationships with collaborators as a result of product acquisitions or strategic positioning resulting from the acquisition;
- cultural challenges associated with integrating employees from the acquired company into our organization;
- the need to implement or improve controls, procedures and policies at a business that prior to the acquisition may have lacked sufficiently effective controls, procedures and policies;
- liability for activities of the acquired company before the acquisition, including intellectual property infringement claims, violation of laws, commercial disputes, tax liabilities and other known liabilities;
- unanticipated write-offs or charges; and
- litigation or other claims in connection with the acquired company, including claims from terminated employees, customers, former stockholders or other third parties.

Our failure to address these risks or other problems encountered in connection with our past or future acquisitions or strategic alliances could cause us to fail to realize the anticipated benefits of these transactions, cause us to incur unanticipated liabilities and harm the business generally. There is also a risk that future acquisitions will result in the incurrence of debt, contingent liabilities, amortization expenses or incremental operating expenses, any of which could harm our financial condition or results of operations.

Our internal information technology systems, or those of our collaborators, vendors or other contractors or consultants, may fail or suffer security breaches, loss of data and other disruptions, which could result in a material disruption of our product development programs, compromise sensitive information related to our business or prevent us from accessing critical information, trigger contractual and legal obligations, potentially exposing us to liability, reputational harm or otherwise adversely affecting our business and financial results.

We are dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information, including but not limited to intellectual property, proprietary business information and personal information. It is critical that we, our vendors, collaborators or other contractors or consultants, do so in a secure manner to maintain the availability, security, confidentiality, privacy and integrity of such confidential information.

Despite the implementation of security measures, our internal information technology systems and those of any collaborators, vendors, contractors or consultants are vulnerable to damage or interruption from computer viruses, computer hackers, malicious code, employee error, theft or misuse, denial-of-service attacks, sophisticated nation-state and nation-state-supported actors, unauthorized access, natural disasters, terrorism, wars or other

armed conflict, telecommunication and electrical failures or other compromise. There could be an increase in cybersecurity attacks generally as a result of the ongoing conflict between Russia and Ukraine and the resulting sanctions imposed by the United States and European governments, together with any additional future sanctions or other actions by them.

Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. We may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies. We cannot guarantee that the measures we have taken to date, and actions we may take in the future, will be sufficient to prevent any future breaches.

To the extent we experience a material system failure, accident, cyber-attack or security breach, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary or confidential information or other disruptions. For example, the loss of clinical trial data from ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information.

To the extent that any disruption or security breach were to result in a loss of, or damage to, our or our vendors', collaborators' or other contractors' or consultants' data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, including litigation exposure, penalties and fines, we could become the subject of regulatory action or investigation, our competitive position and reputation could be harmed and the further development and commercialization of our product candidates could be delayed. As a result of such an event, we may be in breach of our contractual obligations. Furthermore, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our customers or employees, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages. Any of the above could have a material adverse effect on our business, financial condition, results of operations or prospects.

The financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we maintain and could have a material adverse effect on our business, financial condition, results of operations or prospects. In addition, we cannot be sure that our existing insurance coverage will continue to be available on acceptable terms or that our insurers will not deny coverage as to any future claim. There can be no assurance that the limitations of liability in our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above.

Risks related to ownership of our common stock and our status as a public company

Our executive officers, directors and their affiliates, if they choose to act together, will have the ability to significantly influence all matters submitted to stockholders for approval.

Our executive officers and directors and their affiliates, in the aggregate, beneficially owned shares representing approximately 21.0% of our common stock as of January 31, 2023. As a result, if these stockholders were to choose to act together, they would effectively be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and board of directors; or

- delay or prevent a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current directors and members of management.

Provisions in our restated certificate of incorporation and our amended and restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our restated certificate of incorporation or amended and restated bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or the DGCL, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

An active trading market for our common stock may not continue to develop or be sustained.

Our common stock began trading on the Nasdaq Global Select Market on June 17, 2021. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares, or at all.

If securities analysts do not publish or cease publishing research or reports or publish misleading, inaccurate or unfavorable research about our business or if they publish negative evaluations of our stock, the price and trading volume of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. There can be no assurance that existing analysts will continue to cover us or that new analysts will begin to cover us. There is also no assurance that any covering analysts will provide favorable coverage. Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provides more favorable relative recommendations about our competitors, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

The price of our common stock has been volatile and may fluctuate substantially, which could result in substantial losses for our stockholders.

Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- timing and results of or developments in preclinical studies and clinical trials of our product candidates or those of our competitors or potential collaborators;
- adverse regulatory decisions, including failure to receive regulatory approvals for any of our product candidates;
- our success in commercializing our product candidates, if and when approved;
- developments with respect to competitive products or technologies;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property or proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license products, product candidates, technologies, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;
- sales of common stock by us, our executive officers, directors or principal stockholders, or others;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions, such as the impact of the COVID-19 pandemic on our industry and market conditions; and
- the other factors described in this “Risk factors” section.

In the past, following periods of volatility in the market price of a company’s securities, securities class-action litigation has often been instituted against that company. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our offerings or business practices. Such litigation may also cause us to incur other substantial costs to defend such claims and divert management’s attention and resources. Furthermore, negative public announcements of the results of hearings, motions or other interim proceedings or developments could have a negative effect on the market price of our common stock.

We have broad discretion in the use of our cash, cash equivalents, and marketable securities and may not use them effectively.

Our management has broad discretion in the application of our cash, cash equivalents, and marketable securities and could use such funds in ways that do not improve our results of operations or enhance the value of our common stock. 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 stock to decline and delay the development of our product candidates. Pending their use, we may invest these funds in a manner that does not produce income or that loses value.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our IPO continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

In addition, certain of our executive officers, directors and stockholders affiliated with our directors have entered or may enter into Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the executive officer, director or affiliated stockholder when entering into the plan, without further direction from the executive officer, director or affiliated stockholder. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our executive officers, directors and stockholders affiliated with our directors also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Moreover, holders of a substantial number of shares of our common stock have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have also filed registration statements on Form S-8 to register all of the shares of common stock that we were able to issue under our equity compensation plans. Shares registered under these registration statements on Form S-8 can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates, vesting arrangements, and exercise of options.

We are an "emerging growth company" and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an EGC until the end of 2026, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.07 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1 billion of non-convertible debt over a three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive if we rely on certain or all of these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either (i) irrevocably elect to "opt out" of such extended transition period or (ii) no longer qualify as an EGC.

We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management has devoted and will continue to be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, we have incurred and particularly after we are no longer an EGC, we will continue to incur significant legal, accounting and other expenses that we did not previously incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select 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 and will need to continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements, and will make some activities more time-consuming and costly compared to when we were a private company. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting beginning with our filing of this Annual Report on Form 10-K. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

Our restated certificate of incorporation designates the Court of Chancery of the State of Delaware and the federal district courts of the United States of America as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers and employees.

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders;

- any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware; or
- any action asserting a claim arising pursuant to any provision of our restated certificate of incorporation or amended and restated bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine.

These choice of forum provisions will not apply to suits brought to enforce a duty or liability created by the Exchange Act. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our restated certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

These exclusive forum provisions may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees. If a court were to find either exclusive forum provision contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving such action in other jurisdictions, all of which could materially adversely affect our business, financial condition and results of operations.

General risk factors

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. On December 22, 2017, the U.S. government enacted the Tax Act, which significantly reformed the Code. The Tax Act, as amended by the CARES Act, among other things, contains significant changes to corporate taxation, including reducing the corporate tax rate from a top marginal rate of 35% to a flat rate of 21% and limiting the deduction for NOLs arising in taxable years beginning after December 31, 2017 to 80% of current year taxable income. In addition, beginning in 2022, the Tax Act eliminates the option to deduct research and development expenditures currently and generally requires corporations to capitalize and amortize them over five years.

In addition to the CARES Act, as part of Congress' response to the COVID-19 pandemic, economic relief legislation has been enacted in 2020 and 2021 containing tax provisions, and the Inflation Reduction Act, or the IRA, which introduced a number of new tax provisions, was signed into law in August 2022. The IRA in particular imposes a 1% excise tax on certain stock repurchases by publicly traded corporations which generally applies to any acquisition by the publicly traded corporation (or certain of its affiliates) of stock of the publicly traded corporation in exchange for money or other property (other than stock of the corporation itself), subject to a de

minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases. Regulatory guidance under the Tax Act, the IRA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the IRA and additional tax legislation. We urge prospective investors in our common stock to consult with their legal and tax advisors with respect to any recently enacted tax legislation, or proposed changes in law, and the potential tax consequences of investing in or holding our common stock.

Unfavorable global economic conditions could adversely affect our business, financial condition, stock price and results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets and uncertainty about economic stability. The global economy and financial markets may also be adversely affected by the current or anticipated impact of military conflict, including the conflict between Russia and Ukraine, terrorism or other geopolitical events. Sanctions imposed by the United States and other countries in response to such conflicts, including the sanctions relating to Russia, may also adversely impact the financial markets and the global economy, and the economic countermeasures by the affected countries or others could exacerbate market and economic instability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. A severe or prolonged economic downturn could result in a variety of risks to our business, including weakened demand for any product candidates we may develop and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption. If the equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could impair our ability to achieve our growth strategy, could harm our financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that our current or future service providers, manufacturers or other collaborators may not survive such difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget. We cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We currently lease 105,182 square feet of office and laboratory space in Boston, Massachusetts under a lease that expires in December 2032 with an option to extend for an additional five years.

In October 2021, we entered into a sublease agreement with Beam Therapeutics, Inc. for 11,931 square feet of additional office and laboratory space in Cambridge, Massachusetts. The sublease commenced in December 2021 and expired in December 2022.

We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are currently not a party to any material legal proceedings.

From time to time, we may become involved in litigation or other legal proceedings arising in the ordinary course of our business. Regardless of outcome, litigation can have an adverse impact on our business, financial condition, results of operations and prospects because of defense and settlement costs, diversion of management resources and other factors.

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 stock has been publicly traded on the Nasdaq Global Select Market under the symbol "VERV" since June 16, 2021. Prior to that time, there was no public market for our common stock.

Holders

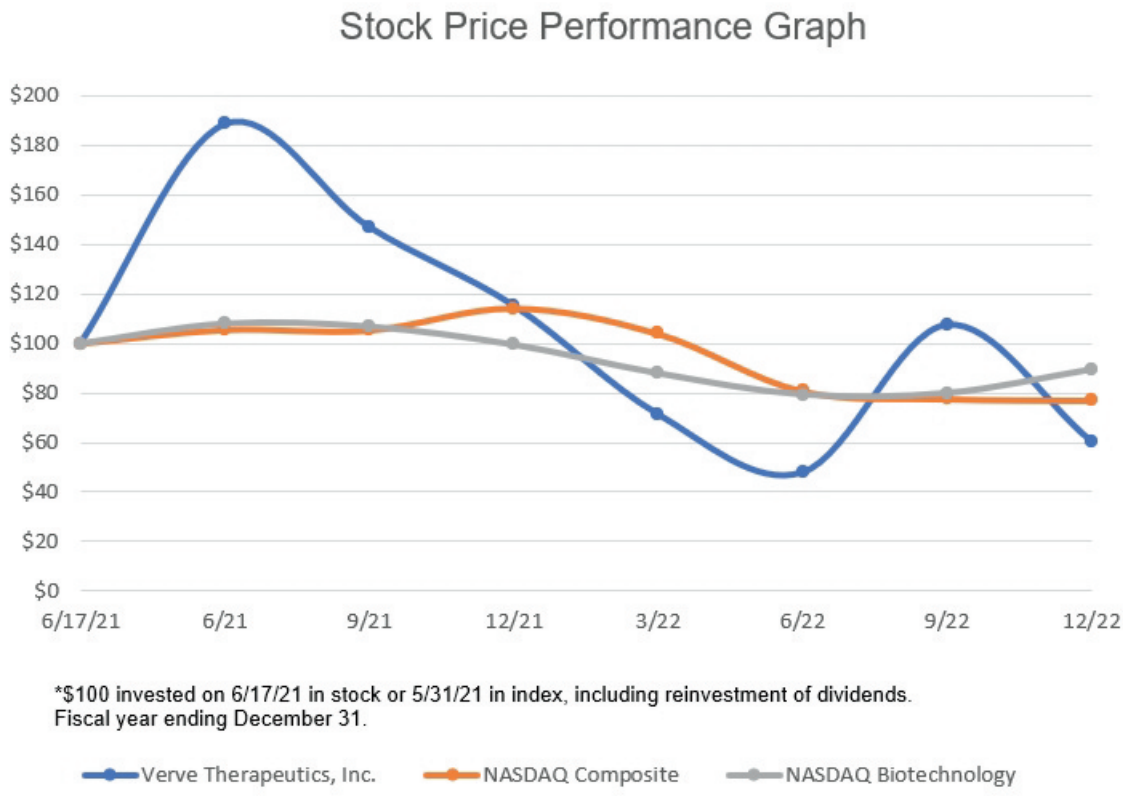
As of February 27, 2023, there were approximately 17 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends to holders of common stock in the foreseeable future.

Stock Performance Graph

The following stock performance graph illustrates a comparison from June 17, 2021 (the date our common stock commenced trading on the Nasdaq Global Select Market) through December 31, 2022, of the total cumulative stockholder return on our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes an initial investment of $ 100 on June 17, 2021 at the opening trading price of $19.00 per share, and that all dividends were reinvested, although dividends have not been declared on our common stock. The comparisons in the graph are required by the SEC and are not intended to forecast or be indicative of possible future performance of our common stock.



The performance graph in this Item 5 is not deemed to be "soliciting material" or to be "filed" with the SEC for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any filing of Verve Therapeutics, Inc. under the Securities Act or the Exchange Act, except to the extent we specifically incorporate it by reference into such a filing.

Recent sales of unregistered securities

During the period covered by this Annual Report on Form 10-K, we did not issue any unregistered equity securities other than pursuant to transactions previously disclosed in our Current Reports on Form 8-K.

Use of proceeds from registered securities

On June 21, 2021, we completed our IPO of common stock pursuant to a Registration Statement on Form S-1 (File No. 333-256608), which was declared effective by the SEC on June 16, 2021 and Form S-1 (File No. 333-257158), which was filed pursuant to Rule 462(b) of the Securities Act and was declared effective by the SEC on June 16, 2021.

The net offering proceeds to us, after deducting underwriting discounts and offering expenses payable by us of $25.1 million, were $281.6 million. As of December 31, 2022, we had not used any of the net proceeds from the IPO. We have invested the net proceeds from the offering in money market funds and short-term investments. There has been no material change in our planned use of the net proceeds from our IPO as described in our final prospectus, dated June 16, 2021, filed with the SEC pursuant to Rule 424(b).

Purchases of equity securities by the issuer or affiliated purchasers

Neither we nor any affiliated purchaser or anyone acting on our behalf or on behalf of an affiliated purchaser made any purchases of shares of our common stock during the year ended December 31, 2022.

Item 6.

[Reserved.]

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

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated financial statements and related notes appearing at the end of this Annual Report on Form 10-K, or the Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, 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, 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 clinical-stage genetic medicines company pioneering a new approach to the care of cardiovascular disease, or CVD, transforming treatment from chronic management to single-course gene editing medicines. Despite advances in treatment over the last 50 years, CVD remains the leading cause of death worldwide. The current paradigm of chronic care is fragile—requiring rigorous patient adherence, extensive healthcare infrastructure and regular healthcare access—and leaves many patients without adequate care. Our goal is to disrupt the chronic care model for CVD by providing a new therapeutic approach with single-course *in vivo* gene editing treatments focused on addressing the root causes of this highly prevalent and life-threatening disease. Our initial two programs target PCSK9 and ANGPTL3, respectively, genes that have been extensively validated as targets for lowering blood lipids, such as low-density lipoprotein cholesterol, or LDL-C. We believe that editing these genes could potently and durably lower LDL-C throughout the lifetimes of patients with or at risk for atherosclerotic cardiovascular disease, or ASCVD, the most common form of CVD.

Our approach leverages multiple breakthroughs in 21st century biomedicine—human genetic analysis, gene editing, messenger RNA, or mRNA, -based therapies and lipid nanoparticle, or LNP, delivery—to target genes that are predominantly expressed in the liver and disrupt the production of proteins that cause CVD. We are advancing a pipeline of single-course *in vivo* gene editing programs, each designed to mimic natural disease resistance mutations and turn off specific genes in order to lower blood lipids, thereby reducing the risk of ASCVD. We intend to initially develop these programs for the treatment of patients with familial hypercholesterolemia, or FH, a genetic disease that causes life-long severely elevated blood LDL-C, leading to increased risk of early-onset ASCVD. If our programs are successful in FH, we believe they could also provide a potential treatment for the broader population of patients with established ASCVD. Ultimately, we believe that these treatments could potentially be developed for administration to people at risk for ASCVD as a preventative measure similar to the way that certain vaccines offer long-term protection against infectious diseases.

We were incorporated in March 2018 and commenced operations shortly thereafter. Since our inception, we have devoted substantially all of our resources to building our gene editing and LNP technology and advancing development of our portfolio of programs, establishing and protecting our intellectual property, conducting research and development activities, organizing and staffing our company, business planning, raising capital and providing general and administrative support for these operations. To date, we have financed our operations primarily through the sales of our preferred stock and through the sale of our common stock in our initial public offering, or IPO, our follow-on public offering, and our at-the-market, or ATM, equity offering program, and through our strategic partnership with Vertex Pharmaceuticals Incorporated, or Vertex.

Through December 31, 2022, we had raised an aggregate of $861.6 million in gross proceeds from sales of our preferred and common stock in private placements and common stock in public offerings.

We are a clinical-stage company. To date, we have not generated any revenue from product sales and do not expect to generate revenue from the sale of products for the foreseeable future. Since our inception, we have incurred significant operating losses. Our net losses for the years ended December 31, 2022, 2021 and 2020 were $157.4 million, $120.3 million and $45.7 million, respectively. As of December 31, 2022, we had an accumulated deficit of $344.2 million.

Our total operating expenses were $167.6 million, $87.1 million and $40.6 million for the years ended December 31, 2022, 2021 and 2020, respectively. We expect to continue to incur significant expenses and increasing operating losses in connection with ongoing development activities related to our portfolio of programs as we advance VERVE-101 in our ongoing heart-1 clinical trial; continue our preclinical development of other

product candidates; advance these product candidates toward clinical development; further develop base editing and novel gene editing technology, delivery technology and manufacturing capabilities; seek to discover and develop additional product candidates including VERVE-201, our development candidate targeting ANGPTL3; maintain, expand enforcement, defend, and protect our intellectual property portfolio; hire research and development and clinical personnel; ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval; establish a commercial manufacturing source and secure supply chain capacity sufficient to provide commercial quantities of any product candidates for which we may obtain regulatory approval; and add operational, legal, compliance, financial and management information systems and personnel to support our research, product development, future commercialization efforts and operations as a public company.

As a result, we will need substantial additional funding to support our continuing operations and pursue our strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings and other sources of capital, which may include collaborations or licensing arrangements with other companies or other strategic transactions. If we are unable to raise capital or obtain adequate funds when needed or on acceptable terms, we may be forced to delay, limit, reduce or terminate our research and development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $554.8 million. We believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2025. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. To finance our operations beyond that point we will need to raise additional capital, which cannot be assured. See “Liquidity and capital resources.”

Impact of COVID-19 on our business

In March 2020, COVID-19 was declared a global pandemic by the World Health Organization and to date, the COVID-19 pandemic continues to present a substantial public health and economic challenge around the world. The length of time and full extent to which the COVID-19 pandemic may directly or indirectly impact our business, results of operations and financial condition will depend on future developments that are highly uncertain, subject to change and difficult to predict. We, our contract manufacturing organizations, or CMOs, and our contract research organizations, or CROs, experienced temporary reductions in the capacity to undertake research-scale production and to execute some preclinical studies. While these operations have since normalized, we, together with our CMOs and CROs, are closely monitoring the impact of the COVID-19 pandemic on these operations.

We also plan to continue to closely monitor the ongoing impact of the COVID-19 pandemic on our employees and our other business operations. In an effort to provide a safe work environment for our employees, we have, among other things, limited employees in our office and lab facilities to those where on-site presence is needed for their job activities, increased the cadence of sanitization of our office and lab facilities, implemented various social distancing measures in our offices and labs including replacing all in-person meetings with virtual interactions, and are providing personal protective equipment for our employees present in our office and lab facilities. Recently, additional employees have returned to our office and lab facilities in limited capacities. We are continuing to monitor the impact and effects of the COVID-19 pandemic and our response to it, and we expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees and other business partners in light of the pandemic.

License and collaboration agreements

We have obligations under various license and collaboration agreements to make potentially significant milestone and success payments in the future and to pay royalties on sales of any product candidates covered by those agreements that eventually achieve regulatory approval and commercialization. For information regarding these agreements, see “Business—License and collaboration agreements” included in Part I, Item 1 of this Annual Report on Form 10-K.

Components of our results of operations

Revenue

For the year ended December 31, 2022, we recognized $1.9 million of collaboration revenue. We do not expect to generate any revenue from the sale of products in the near future and unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates.

Operating expenses

Research and development expenses

Research and development expenses consist of costs incurred in performing research and development activities, which include:

- the cost to obtain and maintain licenses to intellectual property, such as those with the President and Fellows of Harvard College, or Harvard, The Broad Institute, Inc., or Broad, Beam Therapeutics Inc., or Beam, Acuitas Therapeutics, Inc., or Acuitas, and Novartis Pharma AG, or Novartis, and related future payments should certain development and regulatory milestones be achieved;
- costs incurred related to the research pursuant to the Vertex Agreement;
- personnel-related expenses, including salaries, bonuses, benefits and stock-based compensation for employees engaged in research and development functions;
- expenses incurred in connection with the discovery, preclinical and clinical development of our research programs, including under agreements with third parties, such as consultants, contractors and CROs;
- the cost of developing and validating our manufacturing process for use in our preclinical studies and current and future clinical trials, including the cost of raw materials used in our research and development activities;
- the cost of laboratory supplies and research materials; and
- facilities, depreciation and other expenses, which include direct and allocated expenses for rent and maintenance of facilities and insurance.

We expense research and development costs as incurred. Nonrefundable advance payments that we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the benefits are consumed.

In the early phases of development, our research and development costs are often devoted to proof-of-concept studies that are not necessarily allocable to a specific target; therefore, we have not yet begun tracking our expenses on a program-by-program basis.

Research and development activities are central to our business model. We expect that our research and development expenses will continue to increase for the foreseeable future as we advance our programs and product candidates into and through clinical development, develop additional product candidates, build our manufacturing capabilities, and develop our gene editing and LNP technology. We also expect our discovery research efforts and our related personnel costs will increase and, as a result, we expect our research and development expenses, including costs associated with stock-based compensation, will increase above historical levels. In addition, we may incur additional expenses related to milestone and royalty payments payable to third parties with whom we may enter into license, acquisition and option agreements to acquire the rights to future product candidates.

At this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of, and obtain regulatory approval for, any of our product candidates or programs. The successful development of our product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development, including the following:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- raising additional funds necessary to complete preclinical and clinical development of our product candidates;
- the timing of filing and acceptance of investigational new drug, or IND, applications, or comparable foreign applications that allow commencement of planned and future clinical trials for our product candidates;
- the successful initiation, enrollment and completion of clinical trials;

- our ability to achieve positive results from our ongoing and future clinical programs that support a finding of safety and effectiveness and an acceptable risk-benefit profile in the intended patient populations of any product candidates we may develop;
- our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize, our product candidates for the expected indications and patient populations;
- our ability to hire and retain key research and development personnel;
- the costs associated with the development of any additional product candidates we develop or acquire through collaborations;
- our ability to establish and maintain agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if our product candidates are approved;
- the terms and timing of any existing or future collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder;
- our ability to establish and obtain intellectual property protection and regulatory exclusivity for our product candidates and enforce and defend our intellectual property rights and claims;
- our ability to commercialize products, if and when approved, whether alone or in collaboration with others;
- our ability to maintain a continued acceptable safety, tolerability and efficacy profile of our product candidates following approval; and
- the effects of the COVID-19 pandemic.

A change in any of these variables with respect to any of our current or future product candidates could significantly change the costs, timing and viability associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any product candidate we may develop.

General and administrative expenses

General and administrative expenses consist primarily of personnel-related costs, including salaries, benefits and stock-based compensation, for personnel in our executive, intellectual property, business development, and administrative functions. General and administrative expenses also include legal fees relating to intellectual property and corporate matters, professional fees for accounting, auditing, tax and consulting services, insurance costs, travel, and direct and allocated facility-related expenses and other operating costs.

We anticipate that our general and administrative expenses will increase in the future to support increased research and development activities. We also expect to continue to incur increased costs associated with being a public company, including costs of accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with Nasdaq and Securities and Exchange Commission, or SEC, requirements, director and officer insurance costs, and investor and public relations costs.

Other income (expense)

Change in fair value of antidilution rights liability

The antidilution rights represented the obligation to issue additional shares of common stock to Harvard and Broad following the completion of preferred stock financings and other equity financings, which was fully satisfied upon the closing of our IPO. At the inception of the agreements, the liability for the antidilution rights was recorded at fair value with the cost recorded as research and development expense and were remeasured at each reporting period with changes recorded in other income (expense) while the instruments are outstanding.

Change in fair value of success payment liability

We are also obligated to pay to Harvard and Broad tiered success payments in the event our average market capitalization exceeds specified thresholds ascending from a high nine-digit dollar amount to $10.0 billion, or sale of our company for consideration in excess of those thresholds. In the event of a change of control of our company or a sale of our company, we are required to pay any related success payment in cash within a specified period following such event. Otherwise, the success payments may be settled at our option in either cash or shares of our common stock, or a combination of cash and shares of our common stock.The remaining potential aggregate success payments that could be payable by us are $25.0 million. At inception of the agreements, the success payment liabilities were recorded at fair value with the cost recorded as research and development expense and are being remeasured at each reporting period with charges recorded in other income (expense) while the instrument is outstanding.

Depending on our valuation, the fair value of the success payment liability, and the corresponding changes in fair value that we record in our statements of operations, could fluctuate significantly from period to period.

Interest and other income (expense), net

Interest and other income primarily consisted of interest earned on our marketable securities and other miscellaneous income and expenses unrelated to our core operations.

Income tax

As of December 31, 2022, we had federal net operating loss, or NOL, carryforwards of $163.9 million and state NOL carryforwards of $148.0 million. The federal NOL carryforwards have an indefinite life and can be utilized to offset 80% of future taxable income, while the state NOL carryforwards will expire at various dates through 2042. We have recorded a full valuation allowance against our net deferred tax assets due to uncertainties as to their ultimate realization.

Results of operations

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:

	Year ended December 31,		
(in thousands)	**2022**	**2021**	**Change**
Collaboration revenue	$ 1,941	$ —	$ 1,941
Operating expenses:			
Research and development	130,095	68,202	61,893
General and administrative	37,533	18,865	18,668
Total operating expenses	167,628	87,067	80,561
Other (expense) income:			
Change in fair value of antidilution rights liability	—	(25,574)	25,574
Change in fair value of success payment liability	1,486	(7,815)	9,301
Interest and other income, net	6,867	142	6,725
Total other income (expense), net	8,353	(33,247)	41,600
Loss before provision for income taxes	(157,334)	(120,314)	(37,020)
Provision for income taxes	(53)	—	(53)
Net loss	$ (157,387)	$ (120,314)	$ (37,073)

Collaboration Revenue

Collaboration revenue was $1.9 million for the year ended December 31, 2022, all of which related to research services performed under the Vertex Agreement. We did not record any revenue for the year ended December 31, 2021.

Research and development expenses

The following table summarizes our research and development expenses for the years ended December 31, 2022 and 2021:

	Year ended December 31,		
(in thousands)	**2022**	**2021**	**Change**
Employee-related expenses	$ 46,439	$ 19,859	$ 26,580
External expenses associated with preclinical studies performed by outside consultants, including third-party CROs	26,952	17,681	9,271
Raw material costs and external expenses associated with manufacturing activities, including third-party CMOs	20,584	16,628	3,956
Lab supplies	11,883	4,630	7,253
Facility-related costs (including depreciation)	10,486	3,583	6,903
License and milestone payments	4,515	2,031	2,484
Clinical trial costs	3,037	—	3,037
Other research and development costs	6,199	3,790	2,409
Total research and development expenses	$ 130,095	$ 68,202	$ 61,893

Research and development expenses were $130.1 million for the year ended December 31, 2022, compared to $68.2 million for the year ended December 31, 2021. The increase of $61.9 million was primarily due to the growth in our research and development organization to support the advancement of our pipeline and included the following:

- an increase in personnel-related costs of $26.6 million, including an increase in stock-based compensation of $8.7 million, driven by an increase in headcount of employees involved in research and development activities;
- an increase in external expenses associated with preclinical studies (primarily animal-study costs) performed by outside consulting services, including third-party CROs, of $9.3 million;
- an increase in raw material costs and external expenses associated with developing and validating our manufacturing activities, including third-party CMOs, for use in our preclinical studies and clinical trial of $4.0 million;
- an increase in lab supplies of $7.3 million due to the increased investment in research and development activities in 2022;
- an increase in facility-related costs (including depreciation) and other allocated expenses of $6.9 million due to increased investment in research and development as well as additional space leased at 201 Brookline Avenue;
- an increase in research and development expense attributed to license and milestone payments of $2.5 million in 2022;
- an increase in clinical trial costs of $3.0 million associated with our heart-1 clinical trial, a Phase 1b clinical trial of VERVE-101; and
- an increase in other research and development costs of approximately $2.3 million, primarily due to an increase in software, IT, and other miscellaneous charges.

We expect that our research and development expenses will continue to increase for the foreseeable future as we advance our programs and product candidates into and through clinical development, and as we continue to develop additional product candidates and invest in our technology and manufacturing capabilities.

General and administrative expenses

General and administrative expenses were $37.5 million for the year ended December 31, 2022, compared to $18.9 million for the year ended December 31, 2021. The increase of $18.7 million was primarily attributable to the following:

- an increase of $12.9 million in personnel, facility and other expenses, including an increase in stock-based compensation of $6.7 million, resulting from an increase in headcount to support our growth;
- an increase of $3.8 million in legal and professional service fees, primarily due to increased professional fees for audit, tax and consulting services; and
- an increase in other expenses of approximately $2.0 million, including increased insurance expense of $1.3 million for our directors and officers insurance policy and increases in software, IT and other miscellaneous charges.

We anticipate that our general and administrative expenses will increase in the future to support increased research and development activities.

Other income (expense)

Change in fair value of antidilution rights liability

The increase of $25.6 million in fair value of the antidilution rights liability was primarily due to the settlement of the liability during the year ended December 31, 2021 with the issuance of 878,098 shares of our common stock. The settlement amount was $32.5 million and resulted in a fair value adjustment to the antidilution rights liability of $25.6 million due to an increase in the fair value of the shares being issued upon settlement. As the antidilution rights liability was partially satisfied in 2019 and 2020 and was satisfied in full in June 2021 upon the closing of our IPO, there was no further adjustment during the year ended December 31, 2022.

Change in fair value of success payments liability

The increase of $9.3 million in fair value of the success payments liability was primarily attributable to the decrease in the fair value of our common stock which resulted in a fair value adjustment of $1.5 million to other expense during the year ended December 31, 2022. During the year ended December 31, 2021, certain success payment obligations were triggered, and amounts due to Harvard and Broad totaled $6.3 million. These amounts were settled in cash in November 2021. No success payments were triggered or paid during the year ended December 31, 2022. The remaining success payment obligations will continue to be revalued at the end of each reporting period.

Interest and other income (expense), net

The increase of $6.7 million in interest and other income (expense) for the year ended December 31, 2022 was primarily attributable to increasing interest rates on our higher marketable securities balances.

Comparison of the Years Ended December 31, 2021 and 2020

A discussion of changes in our results of operations during the year ended December 31, 2021 compared to the year ended December 31, 2020 has been omitted from this Annual Report on Form 10-K but may be found in “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on March 14, 2022, which discussion is incorporated herein by reference and which is available free of charge on the SEC's website at www.sec.gov.

Liquidity and capital resources

Sources of liquidity and capital

Since our inception in 2018, we have incurred significant operating losses. We expect to incur significant expenses and operating losses for the foreseeable future as we advance the preclinical and clinical development of our programs. To date, we have funded our operations primarily through equity offerings. Through December 31, 2022, we had raised an aggregate of $861.6 million in gross proceeds from sales of our preferred stock and common stock in private placements and common stock in our IPO, our follow-on public offering, and our ATM equity offering program. As of December 31, 2022, we had $554.8 million in cash, cash equivalents and marketable securities.

In June 2021, we completed our IPO in which we issued 16,141,157 shares of common stock, including 2,105,368 shares of common stock sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a public offering price of $19.00 per share. We received net proceeds from our IPO of $281.6 million, after deducting underwriting discounts and offering expenses payable by us. In June 2021, we issued 878,098 shares of our common stock to Harvard and Broad as final settlement of the antidilution rights liability.

On July 20, 2022, we received $25.0 million as an upfront payment from Vertex pursuant to the Vertex Agreement. Additionally, on July 20, 2022, we sold and issued 1,519,756 shares of our common stock to Vertex at a price of $23.03 per share for an aggregate purchase price of $35.0 million.

On July 25, 2022, we issued and sold 9,583,334 shares of our common stock, including 1,250,000 shares of common stock sold pursuant to the underwriters' full exercise of their option to purchase additional shares of common stock, at a public offering price of $27.00 per share, for aggregate net proceeds of approximately $242.9 million after deducting underwriting discounts and offering expenses of approximately $15.9 million payable by us.

In July 2022, we entered into the Sales Agreement with Jefferies pursuant to which we are entitled to offer and sell, from time to time at prevailing market rates, shares of our common stock. We agreed to pay Jefferies a commission of up to 3.0% of the aggregate gross sale proceeds of any shares sold by Jefferies under the Sales Agreement. Any sales under the Sales Agreement will be made pursuant to our registration statement on Form S-3 (File No 333-267578), which became effective on September 23, 2022, with an aggregate offering price of up to $200.0 million. During the year ended December 31, 2022, we sold 1,280,168 shares of common stock under the Sales Agreement for aggregate net proceeds of $42.9 million, after deducting commissions and offering expenses payable by us.

Cash flows

The following table summarizes our sources and uses of cash for each period presented:

	Year ended December 31,	
(in thousands)	**2022**	**2021**
Cash used in operating activities	$ (122,332)	$ (77,880)
Cash used in investing activities	(155,955)	(239,098)
Cash provided by financing activities	328,956	377,089
Net increase in cash, cash equivalents and restricted cash	$ 50,669	$ 60,111

Operating activities

For the year ended December 31, 2022, net cash used in operating activities was $122.3 million, consisting primarily of our net loss of $157.4 million, and a decrease attributable to non-cash items of $1.5 million associated with the fair value change in the success payment liability and $1.0 million associated with amortization of investment premiums. These amounts are partially offset by the following non-cash changes: stock-based compensation of $22.5 million, depreciation expense of $2.8 million, non-cash lease expense of $3.9 million, and a net increase in changes in our operating assets and liabilities of $8.4 million.

For the year ended December 31, 2021, net cash used in operating activities was $77.9 million, consisting primarily of our net loss of $120.3 million and a net decrease in our operating assets and liabilities of $2.9 million. These amounts were partially offset by the following non-cash changes: change in fair value of antidilution rights and success payment liabilities of $33.4 million, depreciation expense of $1.5 million, stock-based compensation of $7.1 million, non-cash lease expense of $1.8 million and amortization of premiums on marketable securities of $1.5 million.

Investing activities

For the year ended December 31, 2022, net cash used in investing activities was $156.0 million, consisting of purchases of marketable securities of $479.4 million and purchases of property and equipment of approximately $13.3 million, primarily related to lab equipment, which amounts were offset partially by maturities of marketable securities of $336.7 million.

For the year ended December 31, 2021, net cash used in investing activities was $239.1 million, consisting of purchases of marketable securities of $371.5 million and purchases of property and equipment of $4.4 million, primarily related to lab equipment, which amounts were offset partially by maturities of marketable securities of $136.8 million.

Financing activities

For the year ended December 31, 2022, net cash provided by financing activities was $329.0 million, consisting primarily of net proceeds from the sale of our common stock of $286.5 million, net proceeds of $40.0 million from the issuance of 1,519,756 shares to Vertex pursuant to the Stock Purchase Agreement in connection with the Vertex Agreement, proceeds from exercises of stock options of $2.2 million and issuance of shares through our employee stock purchase plan of $1.1 million, offset partially by payment of offering expenses of $0.8 million.

For the year ended December 31, 2021, net cash provided by financing activities was $377.1 million consisting of the net proceeds from the issuance of Series B Preferred Stock of $93.8 million, net proceeds from the sale of our common stock in our IPO of $285.2 million, proceeds from exercises of stock options of $1.0 million and issuance of shares through our employee stock purchase plan of approximately $0.7 million, offset partially by payment of IPO expenses of $3.6 million.

Funding requirements

Our operating expenses and future funding requirements are expected to increase substantially as we continue to advance our portfolio of programs.

Specifically, our expenses will increase if and as we:

- conduct our ongoing heart-1 clinical trial for VERVE-101 in New Zealand and the United Kingdom, and if our IND application is cleared, in the United States;
- continue our current research programs and our preclinical development of product candidates;
- seek to identify additional research programs and additional product candidates;
- advance our existing and future product candidates into clinical development;
- initiate preclinical studies and clinical trials for any additional product candidates we identify and develop or expand development of existing programs into additional patient populations;
- maintain, expand, enforce, defend and protect our intellectual property portfolio and provide reimbursement of third-party expenses related to our patent portfolio;
- seek regulatory and marketing approvals for any of our product candidates that we develop;
- perform research services under the Vertex Agreement and seek to identify, establish and maintain additional collaborations and license agreements, and the success of those collaborations and license agreements;
- make milestone payments to Beam under our amended and restated collaboration and license agreement with Beam, or the Beam Agreement, milestone payments to Acuitas under our non-exclusive license agreement with Acuitas, or the Acuitas Agreement, milestone payments or success payments to Broad and Harvard under our license agreement with Broad and Harvard (as amended, the Cas9 License Agreement), and milestone payments to Novartis under our license agreement with Novartis, or the Novartis Agreement, and potential payments to other third parties under our other collaboration agreements or any additional future collaboration or license agreements that we obtain;
- ultimately establish a sales, marketing, and distribution infrastructure to commercialize any drug products for which we may obtain marketing approval, either by ourselves or in collaboration with others;
- further develop our base editing technology and develop novel gene editing technology;
- hire additional personnel including research and development, clinical and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development;
- acquire or in-license products, intellectual property, medicines and technologies;
- satisfy any post-approval marketing requirements, such as a cardiovascular outcomes trial, or CVOT, which we expect will be required for VERVE-101 and VERVE-201;
- establish commercial-scale current good manufacturing practices, or cGMP, capabilities through a third-party or our own manufacturing facility; and
- continue to operate as a public company.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $554.8 million. We believe that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses

and capital expenditure requirements into the second half of 2025. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if ever. Accordingly, we will need to obtain substantial additional funds to achieve our business objectives.

Our expectation with respect to our ability to fund current planned operations is based on estimates that are subject to risks and uncertainties. Our operating plan may change as a result of many factors currently unknown to management and there can be no assurance that the current operating plan will be achieved in the time frame anticipated by us, and we may need to seek additional funds sooner than planned.

Adequate additional funds may not be available to us on acceptable terms, or at all. We do not have any source of committed external funds. Market volatility could also adversely impact our ability to access capital as and when needed. Additional capital raised through the sale of equity or convertible debt securities, may include liquidation or other preferences. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures or declaring dividends and may require the issuance of warrants.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs 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 or other arrangements when needed or on terms acceptable to us, 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.

Contractual obligations

We lease certain assets under noncancelable operating leases, which expire through 2032. The leases relate primarily to office space and laboratory space. Our aggregate future minimum commitments under these office and laboratory leases were $119.2 million as of December 31, 2022, excluding any related common area maintenance charges or real estate taxes. For additional information regarding these leases, refer to Note 7, *Leases*, to our consolidated financial statements.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and manufacturing services. These contracts do not contain minimum purchase commitments and are cancelable by us upon prior written notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation.

We have also entered into license agreements under which we may be obligated to make certain payments. For example, in November 2021, we paid success payments of approximately $6.3 million to Broad and Harvard that were triggered under the Harvard/Broad License Agreement. If additional success payments are triggered, we would be obligated to pay Broad and Harvard up to an additional $25.0 million under the Harvard/Broad License Agreement. Our agreements to license intellectual property include potential milestone payments that are dependent upon the development of products using the intellectual property licensed under the agreements and contingent upon the achievement of development or regulatory approval milestones, as well as commercial and success payment milestones. Such payment obligations are contingent upon the occurrence of future events and the timing and likelihood of such potential obligations are not known. For additional information about our license agreements and amounts that could become payable in the future under such agreements, see “Business—License and collaboration agreements” and Note 8, *License agreements*, to our consolidated financial statements.

Emerging growth company status

As an emerging growth company, or EGC, under the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we may delay the adoption of certain accounting standards until such time as those standards apply to private companies. Other exemptions and reduced reporting requirements under the JOBS Act for EGCs include presentation of only two years of audited financial statements in a registration statement for an IPO, an exemption

from the requirement to provide an auditor's report on internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, an exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation, and less extensive disclosure about our executive compensation arrangements.

In addition, the JOBS Act provides that an EGC can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an EGC to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our consolidated financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We may remain classified as an EGC until the end of the fiscal year ended December 31, 2026, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.07 billion or more in any fiscal year, we would cease to be an emerging growth company as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1 billion of non-convertible debt over a three-year period.

Critical accounting policies and significant judgments

This management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements and related disclosures requires us to make estimates, judgments and assumptions that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2, Summary of significant accounting policies, to our consolidated financial statements, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements:

- revenue recognition
- accrued research and development expenses;
- stock-based compensation and common stock valuation; and
- fair value measurements.

Revenue Recognition

We enter into collaboration agreements which are within the scope of Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers*, or ASC 606, under which we license rights to certain of our product candidates and perform research and development services. The terms of these arrangements typically include payment of one or more of the following: non-refundable, upfront fees; reimbursement of research and development costs; development, regulatory, and commercial milestone payments; and royalties on net sales of licensed products.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, we perform the following five steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) we satisfy each performance obligation. We only apply the five-step model to contracts when it is probable that the entity will collect consideration it is entitled to in exchange for the goods or services it transfers to the customer.

The promised goods or services in our arrangements typically consist of license rights to our intellectual property and research and development services. We provide options to additional items in the contracts, which are accounted for as separate contracts when the customer elects to exercise such options, unless the option provides a material right to the customer. We evaluate the customer options for material rights, or options to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer and are considered distinct when (i) the customer can benefit from the good or service on its own or together with other readily available resources and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct, we consider factors such as the stage of development of the underlying intellectual property, the capabilities of the customer to develop the intellectual property on its own or whether the required expertise is readily available and whether the goods or services are integral or dependent to other goods or services in the contract.

We estimate the transaction price based on the amount expected to be received for transferring the promised goods or services in the contract. The consideration may include fixed consideration or variable consideration. At the inception of each arrangement that includes variable consideration, we evaluate the number of potential payments and the likelihood that the payments will be received. We utilize either the most likely amount method or expected amount method to estimate the amount expected to be received based on which method best predicts the amount expected to be received. The amount of variable consideration which is included in the transaction price may be constrained and is included in the transaction price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period.

Our contracts often include development and regulatory milestone payments which are assessed under the most likely amount method and constrained if it is probable that a significant revenue reversal would occur. Milestone payments that are not within our control or the licensee’s control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraint, and if necessary, adjust its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenues in the period of adjustment. To date, we have not recognized any consideration related to the achievement of development, regulatory, or commercial milestone revenue resulting from any of our collaboration arrangements.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, we have not recognized any consideration related to sales-based royalty revenue resulting from any of our collaboration arrangements.

We allocate the transaction price based on the estimated stand-alone selling price of each of the performance obligations. We must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. We utilize key assumptions to determine the stand-alone selling price for service obligations, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Additionally, in determining the standalone selling price for material rights, we utilize comparable transactions, clinical trial success probabilities, and estimates of option exercise likelihood. Variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated are consistent with the amounts we would expect to receive for the satisfaction of each performance obligation.

The consideration allocated to each performance obligation is recognized as revenue when control is transferred for the related goods or services. For performance obligations which consist of licenses and other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress. We evaluate the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Upfront payments and fees are recorded as deferred revenue upon receipt or when due until we perform our obligations under these arrangements. Amounts are recorded as accounts receivable when our right to consideration is unconditional.

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate certain accrued research and development expenses. This process involves 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 actual costs. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of the estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include those related to fees paid to:

- vendors in connection with discovery and preclinical development activities;
- CROs in connection with clinical trials, preclinical studies and testing; and
- CMOs in connection with the process development and scale up activities and the production of materials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CROs and CMOs that conduct services and supply materials. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. 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. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses. While the majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; some require advance payments. 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 expense. We record these as prepaid expenses on our consolidated balance sheet.

Stock-based compensation

We measure stock options and other stock-based awards granted to employees, directors, consultants or founders based upon their fair value on the date of the grant and recognize stock-based compensation expense over the requisite service period, which is generally the vesting period of the respective award. We recognize forfeitures as they occur.

The stock-based compensation awards are subject to either service or performance-based vesting conditions. We apply the straight-line method of expense recognition to all awards with service-based vesting and recognize stock-based compensation for performance awards based on grant date fair value over the service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

We estimate the fair value of each stock option grant on the date of grant using the Black-Scholes option-pricing model, which uses inputs such as the fair value of our common stock, assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-fee interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. The fair value of our common stock is used to determine the fair value of restricted stock awards.

We estimate the fair value of restricted stock unit awards on the date of grant using the closing price of our common stock on that date.

Prior to our IPO in June 2021, there was no public market for our common stock. As a result, prior to our IPO, the estimated fair value of our common stock was determined by our board of directors as of the date of each option grant, with input from management, considering our most recently available third-party valuations of common stock and our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of grant. Following our IPO, the fair value of our common stock is determined based on the quoted market price of our common stock.

Fair value measurements

Success payments liability

We are required to make success payments to Harvard and Broad in the event our average market capitalization, since the filing of our first Quarterly Report on Form 10-Q, exceeds specified thresholds ascending from a high nine digit dollar amount to $10.0 billion, or sale of our company for consideration in excess of those thresholds. In the event of a change of control of our company or a sale of our company, we are required to pay in cash within a specified period following such event. Otherwise, the payments may be settled at our option in either cash or shares of our common stock, or a combination of cash and shares of our common stock. The success payments are accounted for under ASC 815, *Derivatives and Hedging*, and were initially recorded at fair value with a corresponding charge to research and development expense. Any subsequent changes in fair value are recognized in other income (expense) in the statement of operations. We will continue to adjust the liability for changes in fair value until the earlier of the achievement or expiration of the success payment obligation. To determine the estimated fair value of the success payments, we used a Monte Carlo simulation model, which models the value of the liability based on several key variables, including probability of event occurrence, timing of event occurrence, as well as the value of our common stock.

Recently issued accounting pronouncements

See Note 2, “Summary of significant accounting policies – Recently issued accounting pronouncements” in the accompanying notes to our consolidated financial statements included at the end of this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2022, we had cash and cash equivalents of $115.4 million, which consisted of standard checking accounts and money market account funds that invest primarily in U.S. government-backed securities and treasuries. In addition, as of December 31, 2022, we had marketable securities of $439.4 million, which consist of U.S. treasury securities and agency securities. Interest income is sensitive to change in the general level of interest rates, however, due to the short-term maturities of our cash equivalents and the low risk profile of our marketable securities, an immediate 10% change in interest rates would not have a material effect on the fair market value of our cash equivalents and marketable securities.

Foreign currency exchange risk

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we do contract with vendors that are located outside of the United States and may be subject to fluctuations in foreign currency rates. We may enter into additional contracts with vendors located outside of the United States in the future, which may increase our foreign currency exchange risk.

Inflation

Inflation generally affects us by increasing our cost of labor and target development costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the year ended December 31, 2022.

Item 8. Financial Statements and Supplementary Data.

The financial statements required pursuant to Item 8 are incorporated by reference herein from the applicable information included in Item 15 of this Annual Report on Form 10-K and are presented beginning on page F-1.

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

None.

Item 9A. Controls and Procedures.

Conclusion Regarding the Effectiveness of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Our management, with the participation of our principal executive officer and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act as of the end of the period covered by this annual report. Based on such evaluation, our principal executive officer and principal financial officer have concluded that as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act). Our internal control over financial reporting is a process designed under the supervision of our principal executive and principal financial officer to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Management assessed our internal control over financial reporting as of December 31, 2022. Management based its assessment on criteria established in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework). Based on that evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Attestation Report of the Registered Public Accounting Firm

This annual report does not include an attestation report of our registered public accounting firm due to an exemption provided by the JOBS Act for "emerging growth companies."

Changes in Internal Control Over Financial Reporting

There have been no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the three months ended December 31, 2022, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item 10 will be included in the sections titled “Proposal No. 1—Election of Class II Directors,” “Corporate Governance—Code of business conduct and ethics,” “Corporate Governance—Board committees,” “Corporate Governance—Compensation committee interlocks and insider participation,” and “Delinquent Section 16(a) Reports” (if applicable) in our definitive proxy statement to be filed with the Securities and Exchange Commission, or SEC, with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

We have adopted a written code of business conduct and ethics, or Code, that applies to all of our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the Code is available on the investor section of our website at investors.vervetx.com. We intend to disclose on our website any amendments to, or waivers from, our Code that are required to be disclosed pursuant to SEC rules.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in the section titled “Executive and Director Compensation” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and, other than the information disclosed pursuant to Item 402(v) of Regulation S-K, if required, is incorporated herein by reference.

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

The information required by this Item 12 will be included in the sections titled “Executive and Director Compensation—Equity compensation plan information” and “Security Ownership of Certain Beneficial Owners and Management” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 13 will be included in the sections titled “Transactions with Related Persons” and “Corporate Governance—Director independence” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be included in the section titled “Proposal No. 2—Ratification of Independent Registered Public Accounting Firm” in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

1. **Financial Statements.**

The financial statements of Verve Therapeutics, Inc., together with the report thereon of Ernst & Young LLP, an independent registered public accounting firm (PCAOB ID: 0042), are included in this Annual Report on Form 10-K beginning on page F-1.

2. **Financial Statement Schedules.**

Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

3. **Exhibits**

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of the Registrant, effective as of June 21, 2021 (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, File No. 001-40489, filed June 21, 2021)
3.2	Second Amended and Restated Bylaws of the Registrant, effective as of February 14, 2023 (incorporated by reference to exhibit 3.1 to the Registrant's Current Report on Form 8-K, File No. 001-40489, Filed February 17, 2023.)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28,2021)
4.2	Second Amended and Restated Investors' Rights Agreement, dated as of January 14, 2021, by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
4.3	Description of Securities Registered under Section 12 of the Exchange Act (incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K, filed on March 14, 2022)
10.1#	2018 Equity Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
10.2#	Form of Stock Option Agreement under the 2018 Equity Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
10.3#	2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1, File No. 333-256608, filed June 14, 2021)
10.4#	Form of Stock Option Agreement under the 2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Annual Report on Form 10-K, filed on March 14, 2022)
10.5#*	Form of Restricted Stock Unit Agreement under the 2021 Stock Incentive Plan
10.6#	Amended and Restated 2021 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.7 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1, File No. 333-256608, filed June 14, 2021)
10.7*	Summary of Non-Employee Director Compensation Program
10.8†	Amended and Restated Collaboration and License Agreement, dated as of July 5, 2022, by and between the Registrant and Beam Therapeutics, Inc. (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q, filed on November 7, 2022)
10.9†	Amended and Restated Development and Option Agreement, dated as of October 6, 2020, by and between the Registrant and Acuitas Therapeutics, Inc. (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
10.10†	Non-Exclusive License Agreement, dated as of October 14, 2020, by and between the Registrant and Acuitas Therapeutics, Inc. (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)

10.11†	Cas9 License Agreement, dated as of March 15, 2019, by and among the Registrant, The President and Fellows of Harvard College and The Broad Institute, Inc., as amended (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
10.12†	Strategic Collaboration and License Agreement, dated as of July 18, 2022, by and between the Registrant and Vertex Pharmaceuticals Incorporated (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q, filed on November 7, 2022)
10.13	Lease, dated as of August 19, 2021, by and between the Registrant and ARE-MA Region No. 87 Tenant, LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed on November 10, 2021)
10.14	First Amendment to Lease, dated as of January 4, 2022, by and between the Registrant and ARE-MA Region No. 87 Tenant, LLC (incorporated by reference to Exhibit 10.14 to the Registrant's Annual Report on Form 10-K, filed on March 14, 2022)
10.15	Second Amendment to Lease, dated as of June 17, 2022, by and between the Registrant and ARE-MA Region No, 87 Tenant, LLC (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q, filed on August 9, 2022)
10.16#	Form of indemnification agreement between the Registrant and each of its executive officers and directors (incorporated by reference to Exhibit 10.17 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
10.17#	Employment Agreement, dated as of June 11, 2021, between the Registrant and Sekar Kathiresan, M.D. (incorporated by reference to Exhibit 10.18 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1, File No. 333-256608, filed June 14, 2021)
10.18#	Employment Agreement, dated as of June 11, 2021, between the Registrant and Andrew Ashe, J.D. (incorporated by reference to Exhibit 10.19 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1, File No. 333-256608, filed June 14, 2021)
10.19#	Employment Agreement, dated as of June 11, 2021, between the Registrant and Andrew Bellinger, M.D., Ph.D. (incorporated by reference to Exhibit 10.20 to the Registrant's Amendment No. 1 to Registration Statement on Form S-1, File No. 333-256608, filed June 14, 2021)
10.20#	Employment Agreement, dated as of November 26, 2021, between the Registrant and Allison Dorval (incorporated by reference to Exhibit 10.19 to the Registrant's Annual Report on Form 10-K, filed on March 14, 2022)
10.21	Open Market Sale Agreement[SM],dated as of July 1, 2022, by and between the Registrant and Jefferies LLC (incorporated by reference to Exhibit 1.2 to the Registrant's Registration Statement on Form S-3, File No. 333-265996, filed on July 1, 2022)
10.22*	Stock Purchase Agreement, dated as of July 18, 2022, by and between the Registrant and Vertex Pharmaceuticals Incorporated
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1, File No. 333-256608, filed May 28, 2021)
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm
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 Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2**	Certification of 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.
† Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.
# Indicates management contract or compensatory plan.

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, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

VERVE THERAPEUTICS, INC.

Date: March 2, 2023

By: /s/ Sekar Kathiresan

Sekar Kathiresan
Chief Executive Officer
Principal Executive Officer

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/ Sekar Kathiresan **Sekar Kathiresan**	Chief Executive Officer (Principal Executive Officer)	March 2, 2023
/s/ Allison Dorval **Allison Dorval**	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	March 2, 2023
/s/ Burt Adelman **Burt Adelman**	Director	March 2, 2023
/s/ Lonnel Coats **Lonnel Coats**	Director	March 2, 2023
/s/ Alexander Cumbo **Alexander Cumbo**	Director	March 2, 2023
/s/ Michael MacLean **Michael MacLean**	Director	March 2, 2023
/s/ Sheila Mikhail **Sheila Mikhail**	Director	March 2, 2023
/s/ Krishna Yeshwant **Krishna Yeshwant**	Director	March 2, 2023

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Verve Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Verve Therapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) 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.

Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2021 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases* (Topic 842), and the related amendments.

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 Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our 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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2020.
Boston, Massachusetts
March 2, 2023

Verve Therapeutics, Inc.
Consolidated balance sheets

(in thousands, except share and per share amounts)	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 115,412	$ 64,330
Marketable securities	439,396	296,112
Collaboration receivable	1,012	—
Prepaid expenses and other current assets	7,339	6,686
Total current assets	563,159	367,128
Property and equipment, net	18,778	7,224
Restricted cash	4,824	5,237
Operating lease right-of-use assets	91,877	1,839
Other long term assets	585	2,696
Total assets	$ 679,223	$ 384,124
Liabilities, and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,424	$ 7,077
Accrued expenses	20,767	12,992
Lease liability, current portion	11,904	1,955
Total current liabilities	35,095	22,024
Long-term lease liability	70,014	—
Success payment liability	2,885	4,371
Deferred revenue, non-current	20,014	—
Other long term liabilities	283	377
Total liabilities	128,291	26,772
Commitments and contingencies (See Notes 7 and 8)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized, no shares issued and outstanding	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized, 61,730,816 and 48,511,735 shares issued and outstanding at December 31, 2022 and 2021, respectively	62	49
Additional paid-in capital	895,801	544,381
Accumulated other comprehensive loss	(694)	(228)
Accumulated deficit	(344,237)	(186,850)
Total stockholders' equity	550,932	357,352
Total liabilities, and stockholders' equity	$ 679,223	$ 384,124

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

Verve Therapeutics, Inc.
Consolidated statements of operations and comprehensive loss

(in thousands, except share and per share amounts)	Year ended December 31, 2022	2021	2020
Collaboration revenue	$ 1,941	$ —	$ —
Operating expenses:			
Research and development	130,095	68,202	35,371
General and administrative	37,533	18,865	5,256
Total operating expenses	167,628	87,067	40,627
Loss from operations	(165,687)	(87,067)	(40,627)
Other income (expense):			
Change in fair value of preferred stock tranche liability	—	—	2,507
Change in fair value of antidilution rights liability	—	(25,574)	(5,359)
Change in fair value of success payment liability	1,486	(7,815)	(2,387)
Interest and other income, net	6,867	142	162
Total other income (expense), net	8,353	(33,247)	(5,077)
Loss before provision for income taxes	(157,334)	(120,314)	(45,704)
Provision for income taxes	(53)	—	—
Net loss	$ (157,387)	$ (120,314)	$ (45,704)
Net loss per common share attributable to common stockholders, basic and diluted	$ (2.91)	$ (4.48)	$ (20.31)
Weighted-average common shares used in net loss per share attributable to common stockholders, basic and diluted	54,023,653	26,872,036	2,250,093
Comprehensive Loss:			
Net loss	$ (157,387)	$ (120,314)	$ (45,704)
Other comprehensive loss:			
Unrealized loss on marketable securities	(466)	(236)	(1)
Comprehensive loss	$ (157,853)	$ (120,550)	$ (45,705)

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

Verve Therapeutics, Inc.
Consolidated statements of convertible preferred stock and stockholders' equity (deficit)

(in thousands, except share amounts)	Convertible preferred stock		Common stock		Additional paid-in capital	Accumulated other comprehensive income	Accumulated deficit	Total stockholders' equity (deficit)
	Shares	Amount	Shares	Amount				
Balance at December 31, 2019	51,421,404	$ 25,480	1,854,438	$ 2	$ 1,268	$ 9	$ (20,832)	$ (19,553)
Issuance of Series A convertible preferred stock and settlement of tranche right liability of $7.0 million, net of issuance costs of $22	49,749,167	36,792	—	—	—	—	—	—
Issuance of Series A-2 convertible preferred stock, net of issuance costs of $112	78,348,461	62,888	—	—	—	—	—	—
Additional issuances of common stock to licensor institutions	—	—	187,867	—	487	—	—	487
Vesting of restricted common stock	—	—	537,635	1	—	—	—	1
Unrealized loss on available-for-sale securities	—	—	—	—	—	(1)	—	(1)
Stock-based compensation	—	—	—	—	850	—	—	850
Exercise of stock options	—	—	5,849	—	11	—	—	11
Net loss	—	—	—	—	—	—	(45,704)	(45,704)
Balance at December 31, 2020	179,519,032	$ 125,160	2,585,789	$ 3	$ 2,616	$ 8	$ (66,536)	$ (63,909)
Issuance of Series B convertible preferred stock, net of issuance costs of $241	77,163,022	93,759	—	—	—	—	—	—
Conversion of convertible preferred stock to common stock upon closing of initial public offering	(256,682,054)	(218,919)	27,720,923	28	218,891	—	—	218,919
Issuance of common stock from initial public offering, net of issuance costs of $25,098	—	—	16,141,157	16	281,568	—	—	281,584
Issuance of common stock to licensor institutions	—	—	878,098	1	32,489	—	—	32,490
Vesting of restricted common stock	—	—	537,633	—	—	0	—	—
Exercise of stock options	—	—	599,838	1	965	—	—	966
Purchase of common stock under ESPP	—	—	48,297	—	780	—	—	780
Unrealized loss on available-for-sale securities	—	—	—	—	—	(236)	—	(236)
Stock-based compensation	—	—	—	—	7,072	—	—	7,072
Net loss	—	—	—	—	—	—	(120,314)	(120,314)
Balance at December 31, 2021	—	—	48,511,735	$ 49	$ 544,381	$ (228)	$ (186,850)	$ 357,352
Exercise of stock options	—	—	743,638	—	2,175	—	—	2,175
Vesting of restricted stock units	—	—	6,375	—	—	—	—	—
Purchase of common stock under ESPP	—	—	85,810	—	1,069	—	—	1,069
Issuance of common stock in connection with the Vertex Agreement	—	—	1,519,756	2	39,984	—	—	39,986
Issuance of common stock upon follow-on public offering, net of issuance costs of $15,924	—	—	9,583,334	10	242,816	—	—	242,826
Issuance of common stock from At-the-Market offering, net of issuance costs of $1,722	—	—	1,280,168	1	42,899	—	—	42,900
Unrealized loss on available-for-sale securities	—	—	—	—	—	(466)	—	(466)
Stock-based compensation			—	—	22,477	—	—	22,477
Net loss	—	—	—	—	—	—	(157,387)	(157,387)
Balance at December 31, 2022	—	—	61,730,816	$ 62	$ 895,801	$ (694)	$ (344,237)	$ 550,932

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

Verve Therapeutics, Inc.
Consolidated statements of cash flows

(in thousands)	Year ended December 31, 2022	2021	2020
Cash flows from operating activities:			
Net loss	$ (157,387)	$ (120,314)	$ (45,704)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	2,804	1,535	1,328
Non-cash lease expense	3,907	1,842	—
Net amortization of premium (accretion of discount) on marketable securities	(1,027)	1,508	380
Stock-based compensation	22,477	7,072	850
Change in fair value of preferred stock tranche liabilities	—	—	(2,507)
Change in fair value of antidilution rights	—	25,574	5,359
Change in fair value of success payments liabilities	(1,486)	7,815	2,387
Changes in operating assets and liabilities:			
Collaboration receivable	(1,012)	—	—
Prepaid expenses and other current assets	(9,436)	(7,528)	(1,582)
Accounts payable	(5,216)	6,829	(1,898)
Accrued expenses and other liabilities	7,041	5,977	6,071
Success payment liability	—	(6,250)	—
Deferred revenue	20,014	—	—
Operating lease liabilities	(3,011)	(1,940)	—
Deferred rent liability	—	—	51
Net cash used in operating activities	(122,332)	(77,880)	(35,265)
Cash flows from investing activities:			
Purchases of property and equipment	(13,232)	(4,359)	(3,424)
Purchases of marketable securities	(479,401)	(371,494)	(98,484)
Maturities of marketable securities	336,678	136,755	50,781
Net cash used in investing activities	(155,955)	(239,098)	(51,127)
Cash flows from financing activities			
Proceeds from issuance of Preferred Stock, net	—	93,759	92,616
Proceeds from issuance of common stock, net of issuance costs	286,509	285,214	—
Proceeds from the issuance of common stock in connection with the Vertex Agreement	39,986	—	—
Payment of equity offering costs	(783)	(3,630)	—
Proceeds from exercise of stock options	2,175	966	11
Proceeds from purchase of shares through employee stock purchase plan	1,069	780	—
Net cash provided by financing activities	328,956	377,089	92,627
Increase in cash, cash equivalents and restricted cash	50,669	60,111	6,235
Cash, cash equivalents and restricted cash—beginning of period	69,567	9,456	3,221
Cash, cash equivalents and restricted cash—end of period	$ 120,236	$ 69,567	$ 9,456
Supplemental disclosure of noncash investing and financing activities:			
Property and equipment additions included in accounts payable and accrued expenses	$ 1,706	$ 503	$ 86
Settlement of tranche right liability	$ —	$ —	$ 7,064
Conversion of convertible preferred stock to common stock upon closing of initial public offering	$ —	$ 218,919	$ —
Settlement of derivative liability by issuing common stock	$ —	$ 32,490	$ 487
Right-of-use assets obtained in exchange for new operating lease liabilities	$ 83,417	$ 809	$ —

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

Verve Therapeutics, Inc.
Notes to consolidated financial statements

1. Nature of the business and basis of presentation

Organization

Verve Therapeutics, Inc. (the "Company" or "Verve") is a clinical-stage genetic medicines company pioneering a new approach to the care of cardiovascular disease, transforming treatment from chronic management to single-course gene editing medicines. The Company was incorporated on March 9, 2018 as Endcadia, Inc., a Delaware corporation, and began operations shortly thereafter. In January 2019, the Company amended its certificate of incorporation to change its name to Verve Therapeutics, Inc. The Company's principal offices are located in Boston, Massachusetts.

Liquidity and capital resources

Since its inception, the Company has devoted its efforts principally to research and development and raising capital. The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry including, but not limited to, technical risks associated with the successful research, development and manufacturing of product candidates, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Current and future programs will require significant research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The accompanying consolidated financial statements have been prepared on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. The Company expects that its cash, cash equivalents and marketable securities of $554.8 million as of December 31, 2022, will be sufficient to fund its operations and capital expenditure requirements beyond the next 12 months from the date of issuance of these financial statements. The Company will need additional financing to support its continuing operations and pursue its growth strategy. Until such time as the Company can generate significant revenue from product sales, if ever, it expects to finance its operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. The Company may be unable to raise additional funds or enter into such other agreements when needed on favorable terms or at all. The inability to raise capital as and when needed could have a negative impact on the Company's financial condition and its ability to pursue its business strategy. The Company will need to generate significant revenue to achieve profitability, and it may never do so.

Basis of presentation

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

2. Summary of significant accounting policies

Principles of consolidation

The accompanying consolidated financial statements include the accounts of Verve and its wholly owned subsidiary, Verve Securities Corporation. All intercompany transactions and balances have been eliminated in consolidation.

Use of estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities and expenses, and the disclosure of contingent assets and liabilities as of and during the reporting period. The Company bases its estimates and assumptions on historical experience when available and on various factors that it believes to be reasonable under the

circumstances. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the fair values of common stock (prior to completion of the Company's initial public offering ("IPO")), stock-based compensation, and the liabilities for antidilution rights and success payments. Actual results could differ from these estimates.

Cash and cash equivalents

Cash and cash equivalents consist of standard checking accounts and money market account funds that invest primarily in U.S. government-backed securities and treasuries. The Company considers all highly liquid investments with an original maturity of three months or less at the date of purchase to be cash equivalents. Cash equivalents are stated at cost, which is substantially equivalent to fair value.

Restricted cash

Restricted cash represents collateral provided for a letter of credit issued as a security deposit in connection with the Company's leases of its corporate facilities. A reconciliation of the cash, cash equivalents, and restricted cash reported within the balance sheet that sum to the total of the same amounts shown in the statement of cash flows is as follows:

	December 31,	
(in thousands)	**2022**	**2021**
Cash and cash equivalents	$ 115,412	$ 64,330
Restricted cash	4,824	5,237
Total cash, cash equivalents and restricted cash	$ 120,236	$ 69,567

Marketable securities

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Available-for-sale securities are maintained by the Company's investment managers and consist of U.S. treasury bills and U.S agency securities. The Company classifies investments available to fund current operations as current assets on its consolidated balance sheets. Available-for-sale securities are carried at fair value with the unrealized gains and losses included in accumulated other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the instrument. Realized gains and losses are determined using the specific identification method and are included in other income (expense).

The Company reviews marketable securities for other-than-temporary impairment whenever the fair value of a marketable security is less than the amortized cost and evidence indicates that a marketable security's carrying amount is not recoverable within a reasonable period of time. Other-than-temporary impairments of investments are recognized in the consolidated statements of operations if the Company has experienced a credit loss, has the intent to sell the marketable security, or if it is more likely than not that the Company will be required to sell the marketable security before recovery of the amortized cost basis. Evidence considered in this assessment includes reasons for the impairment, compliance with the Company's investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period. The Company evaluated its securities for other-than-temporary impairment and considered the decline in market value for the securities to be primarily attributable to current economic and market conditions. It is not more likely than not that the Company will be required to sell the securities, and the Company does not intend to do so prior to the recovery of the amortized cost basis. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of December 31, 2022 and 2021.

Concentrations of credit risk

Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash, cash equivalents, marketable securities, and restricted cash. Periodically, the Company may maintain deposits in financial institutions in excess of government insured limits. Management believes that the Company is not exposed to significant credit risk as the Company's deposits are held at financial institutions that management believes to be of high credit quality, and the Company has not experienced any losses on these deposits.

The Company generally invests its excess capital in money market funds, U.S. treasury bills and agency securities, all of which are subject to minimal credit and market risk. The investment portfolio is maintained in

accordance with the Company's investment policy, which defines allowable investments, specifies credit quality standards and limits the credit exposure of any single issuer.

Deferred offering costs

The Company capitalized incremental legal, professional accounting and other third-party fees that were directly associated with the stock offerings as other non-current assets until the offerings were consummated. After consummation of the offerings, these costs were recorded in stockholders' equity (deficit) as a reduction of additional paid-in capital generated as a result of the offering.

Fair value of financial instruments

ASC Topic 820, *Fair Value Measurement* ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the assets or liability and are developed based on the best information available in the circumstances. ASC 820 identifies fair value as the price that would be received to sell an asset or paid to transfer a liability, in an orderly transaction between market participants at the measurement date. As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tiered value hierarchy that distinguishes between the following:

Level 1—Quoted market prices in active markets for identical assets or liabilities.

Level 2—Inputs other than Level 1 inputs that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.

Level 3—Unobservable inputs for the asset or liability (i.e. supported by little or no market activity). Level 3 inputs include management's own assumptions about the assumptions that market participants would use in pricing the asset or liability (including assumptions about risk).

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

There have been no changes to the valuation methods utilized by the Company during the years ended December 31, 2022, 2021 and 2020. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of financial instruments between levels during the years ended December 31, 2022 and 2021.

Property and equipment, net

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight-line method over the estimated useful life of each asset as follows:

Asset category	Estimated useful life
Computer equipment and software	3 years
Office furniture	4 years
Laboratory equipment	5 years
Leasehold improvements	Shorter of useful life or remaining lease term

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in loss from operations. Expenditures for repairs and maintenance are charged to expense as incurred.

Impairment of long-lived assets

The Company evaluates its long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be

recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. There were no impairment losses recognized during the years ended December 31, 2022, 2021 and 2020.

Freestanding financial instruments and derivatives

The Company has identified the following financial instruments, which are recorded as liabilities in the balance sheet and separately accounted for at fair value.

Preferred Stock Tranche Liabilities—The Company has determined that its obligation to issue, and the Company's investors' right to purchase, additional shares of convertible Series A Preferred Stock ("Series A Preferred") pursuant to subsequent closings represent a freestanding financial instrument. The freestanding preferred stock tranche liability (the "tranche liability") was initially recorded at fair value, with gains and losses arising from changes in fair value recognized in other income (expense) in the statement of operations and comprehensive loss. The tranche liabilities were remeasured at each reporting period and upon the exercise or expiration of the obligation. As of December 31, 2020, all Series A Preferred closings occurred, and all preferred stock tranche liabilities were settled. Refer to Note 9, Preferred Stock tranche liability, for additional discussion.

Pursuant to license agreements with (i) the President and Fellows of Harvard College ("Harvard") and The Broad Institute, Inc. ("Broad") ("Harvard/Broad License Agreement") and (ii) Broad ("Broad License Agreement") (see Note 8, License agreements), the following financial instruments were issued by the Company.

Antidilution Rights—The antidilution rights represented the obligation to issue additional shares of common stock to Harvard and Broad following the completion of additional financings, including the Company's initial public offering. These antidilution rights were accounted for under ASC 815, *Derivatives and Hedging* ("ASC 815"), and were initially recorded at fair value with a corresponding charge to research and development expense. The liability was remeasured at each reporting period, with changes in fair value recognized in other income (expense) in the statement of operations and comprehensive loss while this instrument was outstanding. The obligation was satisfied in full upon the issuance of an aggregate of an additional 878,098 shares of common stock upon the closing of the Company's IPO in June 2021. Refer to Note 5, Fair value of financial instruments, for additional discussion.

Success Payments—The Company is obligated to pay to Harvard and Broad tiered success payments in the event the Company's average market capitalization exceeds specified thresholds ascending from a high nine digit dollar amount to $10.0 billion, or sale of the Company for consideration in excess of those thresholds. In the event of a change of control of the Company or a sale of the Company, the Company is required to pay in cash within a specified period following such event. Otherwise, the payments may be settled at the Company's option in either cash or shares of the Company's common stock. The success payments are accounted for under ASC 815 and were initially recorded at fair value with a corresponding charge to research and development expense. The liability is remeasured at each reporting period with all changes in value recognized in other income (expense) in the statement of operations and other comprehensive loss. During the year ended December 31, 2021, certain success payment obligations were triggered, and amounts paid to Harvard and Broad totaled $6.3 million. These amounts were settled in cash in November 2021. No success payments were triggered or paid during the year ended December 31, 2022. The Company will continue to adjust the liability for changes in fair value until the earlier of the achievement or expiration of the remaining success payment obligation. Refer to Note 5, Fair value of financial instruments, for additional discussion.

Revenue Recognition

The Company enters into collaboration agreements which are within the scope of ASC Topic 606, "Revenue from Contracts with Customers" ("ASC 606"), under which the Company licenses rights to certain of the Company's product candidates and performs research and development services. The terms of these arrangements typically include payment of one or more of the following: non-refundable, upfront fees; reimbursement of research and development costs; development, regulatory, and commercial milestone payments; and royalties on net sales of licensed products.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, the Company performs the following five steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The

Company only applies the five-step model to contracts when it is probable that the entity will collect consideration it is entitled to in exchange for the goods or services it transfers to the customer.

The promised goods or services in the Company's arrangements typically consist of license rights to the Company's intellectual property and research and development services. The Company provides options to additional items in the contracts, which are accounted for as separate contracts when the customer elects to exercise such options, unless the option provides a material right to the customer. The Company evaluates the customer options for material rights, or options to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. Performance obligations are promised goods or services in a contract to transfer a distinct good or service to the customer and are considered distinct when (i) the customer can benefit from the good or service on its own or together with other readily available resources and (ii) the promised good or service is separately identifiable from other promises in the contract. In assessing whether promised goods or services are distinct, the Company considers factors such as the stage of development of the underlying intellectual property, the capabilities of the customer to develop the intellectual property on its own or whether the required expertise is readily available and whether the goods or services are integral or dependent to other goods or services in the contract.

The Company estimates the transaction price based on the amount expected to be received for transferring the promised goods or services in the contract. The consideration may include fixed consideration or variable consideration. At the inception of each arrangement that includes variable consideration, the Company evaluates the number of potential payments and the likelihood that the payments will be received. The Company utilizes either the most likely amount method or expected amount method to estimate the amount expected to be received based on which method best predicts the amount expected to be received. The amount of variable consideration which is included in the transaction price may be constrained and is included in the transaction price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period.

The Company's contracts often include development and regulatory milestone payments which are assessed under the most likely amount method and constrained if it is probable that a significant revenue reversal would occur. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such development milestones and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenues in the period of adjustment. To date, the Company has not recognized any consideration related to the achievement of development, regulatory, or commercial milestone revenue resulting from any of the Company's collaboration arrangements.

For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any consideration related to sales-based royalty revenue resulting from any of the Company's collaboration arrangements.

The Company allocates the transaction price based on the estimated stand-alone selling price of each of the performance obligations. The Company must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the stand-alone selling price for service obligations, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Additionally, in determining the standalone selling price for material rights, the Company utilizes comparable transactions, clinical trial success probabilities, and estimates of option exercise likelihood. Variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated are consistent with the amounts the Company would expect to receive for the satisfaction of each performance obligation.

The consideration allocated to each performance obligation is recognized as revenue when control is transferred for the related goods or services. For performance obligations which consist of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate

method of measuring progress. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Upfront payments and fees are recorded as deferred revenue upon receipt or when due until the Company performs its obligations under these arrangements. Amounts are recorded as accounts receivable when the Company's right to consideration is unconditional.

Research and development costs

Research and development costs are charged to expense as incurred. Research and development costs consist of costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, facilities costs, third-party license fees related to technology with no alternative future use, laboratory supplies, depreciation, manufacturing expenses, preclinical, clinical and regulatory expenses, consulting and other contracted services. Costs for certain research and development activities are recognized based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development.

Stock-based compensation

The Company's stock-based compensation program allows for grants of certain equity awards. Grants are awarded to employees and non-employees, including directors.

The Company accounts for its stock-based compensation in accordance with ASC Topic 718, *Compensation-Stock Compensation* (''ASC 718''). ASC 718 requires all stock-based payments to employees, non-employees and directors, to be recognized as expense in the consolidated statements of operations and comprehensive loss based on their grant date fair values. The Company estimates the fair value of options granted using the Black-Scholes option pricing model (''Black-Scholes'') for stock option grants to both employees and non-employees. The fair value of the Company's common stock is used to determine the fair value of restricted stock unit awards. The Company estimates the fair value of the Company's restricted stock unit awards on the date of grant using the closing price of the Company's common stock on that date.

The Company's stock-based compensation awards are subject to either 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 over the implied service period when achievement of the performance-based milestones is deemed probable. The Company uses judgement to determine whether and, if so, how many awards are deemed probable of vesting at each reporting period.

The estimation of fair value for stock-based compensation requires management to make estimates and judgments about, among other things, the estimated life of options and volatility of the Company's common stock. The judgments directly affect the amount of compensation expense that will be recognized.

Prior to the Company's IPO in June 2021, there was no public market for its common stock. As a result, prior to the IPO, the estimated fair value of the Company's common stock was determined by its board of directors as of the date of each option grant, with input from management, considering the Company's most recently available third-party valuations of common stock and its board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of grant. Following the Company's IPO, the fair value of its common stock is determined based on the closing price of the Company's common stock as reported on the Nasdaq Global Select Market.

Leases

During the quarter ended September 30, 2021, the Company early adopted ASC Topic 842, "Leases" ("ASC 842") using the revised modified retrospective approach, which uses the effective date, or January 1, 2021, as the date of initial application. As a result, prior periods are presented in accordance with the previous guidance in ASC 840. As a result of the adoption of ASC 842, the Company recorded (i) an operating lease liability of $2.6 million determined using an incremental borrowing rate as of the effective adoption date and (ii) an operating lease right-of-use asset of $2.4 million, net of the unamortized balance of prepaid/accrued rent as of the transition date. There was no impact to the Company's results of operations and cash flows from operations.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on specific facts and circumstances, the existence of an identified asset(s), if any, and the Company's control over the use of the identified asset(s), if applicable. If an arrangement is determined to be or contain a lease, the lease is assessed for classification as either an operating or finance lease at the lease commencement date, defined as the date on which the leased asset is made available for use by the Company, based on the economic characteristics of the lease. The lease liability is measured at the present value of future lease payments, discounted using the discount rate as of the lease commencement date. The interest rate implicit in lease contracts is typically not readily determinable. As such, the Company utilizes the incremental borrowing rate, which is the rate incurred to borrow, on a collateralized basis over a similar term, an amount equal to the lease payments in a similar economic environment. The Company recognizes a corresponding lease right of use ("ROU") asset, initially measured as the amount of lease liability, adjusted for any initial lease costs or lease payments made before or at the commencement of the lease, and reduced by any lease incentives.

The Company's leases consist of only operating leases. Operating leases are recognized on the balance sheet as ROU lease assets, lease liabilities current and lease liabilities non-current. Fixed rents are included in the calculation of the lease balances while certain variable costs paid for certain operating and pass-through costs are excluded. Lease expense is recognized over the expected term on a straight-line basis.

Income taxes

The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the Company's financial statements and tax returns. Deferred tax assets and liabilities are determined based upon the differences between the financial statement carrying amounts and the tax bases of existing assets and liabilities and for loss and credit carryforwards, using enacted tax rates expected to be in effect in the year in which the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance if it is more likely than not that these assets may not be realized. The Company determines whether it is more likely than not that a tax position will be sustained upon examination. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The tax benefit to be recognized for any tax position that meets the more-likely-than-not recognition threshold is calculated as the largest amount that is more than 50% likely of being realized upon resolution of the contingency. The Company accounts for interest and penalties related to uncertain tax positions as part of its provision for income taxes.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2022, 2021 and 2020, the Company's only element of other comprehensive loss was unrealized losses on marketable securities.

Net loss per share

The Company follows the two-class method when computing net loss per share, as the Company has issued shares that meet the definition of participating securities. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net loss per share attributable to common stockholders is computed by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net loss attributable to common stockholders is computed by adjusting net loss attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of common stock equivalents.

The Company's convertible preferred stock contractually entitled the holders of such shares to participate in dividends but did not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is

anti-dilutive. The Company reported a net loss attributable to common stockholders for the years ended December 31, 2022, 2021 and 2020.

Segment and geographic information

Operating segments are defined as components of an entity about which separate discrete information is available for evaluation by the chief operating decision maker ("CODM"), or decision-making group, in deciding how to allocate resources and in assessing performance. The CODM is the Company's Chief Executive Officer. The Company views its operations as and manages its business in one operating segment operating exclusively in the United States.

Subsequent events

The Company performs an evaluation of all subsequent events after the balance sheet date through the date of issuance of the consolidated financial statements to ensure appropriate disclosure of events both recognized in the consolidated financial statements and events which occurred subsequently but were not recognized in the consolidated financial statements.

Recently issued accounting pronouncements

The Jumpstart Our Business Startups Act of 2012 permits an emerging growth company ("EGC") to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. As an EGC, the Company has elected to take advantage of this extended transition period for certain new accounting standards.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses* (Topic 326): Measurement of Credit Losses on Financial Instruments. The standard requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For available-for-sale debt securities with unrealized losses, this standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard became effective for the Company on January 1, 2023. Based on composition of the Company's investment portfolio, current market conditions, and historical credit loss activity, the Company does not expect the adoption of this standard to have a material impact on the consolidated financial statements and related disclosures.

3. Marketable securities

Marketable securities by security type consisted of the following:

	December 31, 2022			
(in thousands)	Amortized cost	Gross unrealized gains	Gross unrealized losses	Fair value
U.S. treasury bills and notes	$ 228,432	$ 13	$ (301)	$ 228,144
U.S. agency securities	211,658	68	(474)	211,252
Total	$ 440,090	$ 81	$ (775)	$ 439,396

	December 31, 2021			
(in thousands)	Amortized cost	Gross unrealized gains	Gross unrealized losses	Fair value
U.S. treasury bills and notes	$ 277,559	$ —	$ (218)	$ 277,341
U.S. agency securities	18,781	—	(10)	18,771
Total	$ 296,340	$ —	$ (228)	$ 296,112

The remaining contractual maturities of all marketable securities were less than 18 months as of December 31, 2022 and 2021.The unrealized losses on the Company's marketable securities of $0.8 million and $0.2 million as of December 31, 2022 and 2021, respectively, were caused by interest rate increases which resulted in the decrease in market value of these securities. Because the decline in fair value is attributable to changes in interest rates and not credit quality, and because the Company does not intend to sell the investments and it is not more likely than not that the Company will be required to sell the investments before recovery of their amortized cost bases, which may be maturity, the Company does not consider those marketable securities to be

other-than-temporarily impaired at December 31, 2022 or 2021. None of the Company's marketable securities have been in a continuous unrealized loss position for 12 months or greater as of December 31, 2022 or 2021.

4. Property and equipment, net

Property and equipment, net, consist of the following:

	December 31,	
(in thousands)	2022	2021
Lab equipment	20,379	$ 8,567
Leasehold improvements	266	266
Furniture and fixtures	2,294	566
Computer equipment	826	158
Total property and equipment	23,765	9,557
Less accumulated depreciation	(4,987)	(2,333)
Property and equipment, net	$ 18,778	$ 7,224

	Year ended December 31,		
(in thousands)	2022	2021	2020
Depreciation expense	$ 2,804	$ 1,535	$ 1,328

5. Fair value of financial instruments

The Company's financial instruments that are measured at fair value on a recurring basis consist of money market funds, marketable securities, and a derivative liability (success payment liability) pursuant to the Harvard/ Broad License Agreement and the Broad License Agreement. The antidilution right liability was fully settled in the year ended December 31, 2021. The following tables set forth the fair value of the Company's financial instruments by level within the fair value hierarchy:

	As of December 31, 2022			
(in thousands)	Fair value	Level 1	Level 2	Level 3
Assets				
Money market funds	$ 105,303	$ 105,303	$ —	$ —
Marketable securities:				
U.S. treasury bills and notes	228,144	—	228,144	—
U.S. agency securities	211,252	—	211,252	—
Total assets	$ 544,699	$ 105,303	$ 439,396	$ —
Liabilities				
Success payment liability	2,885	—	—	2,885
Total liabilities	$ 2,885	$ —	$ —	$ 2,885

	As of December 31, 2021			
(in thousands)	Fair value	Level 1	Level 2	Level 3
Assets				
Money market funds	$ 58,127	$ 58,127	$ —	$ —
Marketable securities:				
U.S. treasury bills and notes	277,341	—	277,341	—
U.S. agency securities	18,771	—	18,771	—
Total assets	$ 354,239	$ 58,127	$ 296,112	$ —
Liabilities				
Success payment liability	$ 4,371	$ —	$ —	$ 4,371
Total liabilities	$ 4,371	$ —	$ —	$ 4,371

Cash Equivalents—Cash equivalents of $105.3 million and $58.1 million as of December 31, 2022 and 2021, respectively, consisted of money market funds and are classified within Level 1 of the fair value hierarchy because they are valued using quoted market prices in active markets.

Marketable Securities—The Company measures its marketable securities at fair value on a recurring basis and classifies those instruments within Level 2 of the fair value hierarchy. Marketable securities are classified within Level 2 of the fair value hierarchy because pricing inputs are other than quoted prices in active markets, which are either directly or indirectly observable as of the reporting date, and fair value is determined through the use of models or other valuation methodologies.

Antidilution Rights—This obligation was satisfied in full upon the issuance of an aggregate of an additional 878,098 shares of common stock upon the closing of the Company's IPO in June 2021. Refer to Note 5, Fair value of financial instruments, for additional discussion.

Success Payment Liability— The Company is obligated to pay to Harvard and Broad tiered success payments in the event its average market capitalization exceeds specified thresholds for a specified period of time ascending from a high nine-digit dollar amount to $10.0 billion, or sale of the Company for consideration in excess of those thresholds. In the event of a change of control or a sale of the Company, the Company is required to pay success payments in cash within a specified period following such event. Otherwise, the success payments may be settled at the Company's option in either cash or shares of its common stock, or a combination of cash and shares of its common stock. The maximum aggregate success payments that could be payable by the Company is $31.3 million (after termination of the Broad License Agreement).

The success payments liability is stated at fair value and is considered Level 3 because its fair value measurement is based, in part, on significant inputs not observed in the market. The Company used a Monte Carlo simulation model, which models the value of the liability based on several key variables, including probability of event occurrence, timing of event occurrence, as well as the value of the Company's common stock.

The Company remeasured the liability at fair value with increases of $1.5 million, $7.8 million and $2.4 million recorded to other expense for the years ended December 31, 2022, 2021 and 2020, respectively.

In September 2021, multiple success payments were triggered and amounts due to Harvard and Broad totaled $6.3 million. These amounts were settled in cash in November 2021. The Company will continue to adjust the remaining success payment liability for changes in fair value until the earlier of the achievement or expiration of the obligation.

The primary inputs used in valuing the success payments liability associated with the Company's realization of a certain valuation threshold through either a sale of the Company's preferred stock, an initial public offering, or a company sale at December 31, 2022, 2021 and 2020, were as follows:

	At December 31, 2022	At December 31, 2021	At December 31, 2020
Fair value of common stock (per share)	$ 19.35	$ 36.87	$ 8.24
Equity volatility	84%	77%	105%
Cumulative probability of triggering event	n/a	n/a	70%
Expected term (in years)	n/a	n/a	0.50

At December 31, 2020 the fair value of the Company's common stock was determined by management with the assistance of an independent third-party valuation specialist using methods consistent with the AICPA Valuation Guide. The computation of equity volatility was estimated using available information about the historical volatility of stocks of similar publicly traded companies for a period matching the expected term assumption. In addition, the Company incorporated the timing and probability of future events in the calculation of liabilities. The Company applied a 90% probability of termination of the Broad License Agreement at December 31, 2020.

In February 2021, the Company provided written notice to Broad of its election to terminate the Broad License Agreement, which termination became effective in June 2021.

The reconciliation of changes in the fair value of financial instruments based on Level 3 inputs were as follows:

(in thousands)	Antidilution rights liability	Success payment liability	Total
Balance at December 31, 2020	$ 6,916	$ 2,806	$ 9,722
Issuance of Series A Preferred	(32,490)	—	(32,490)
Issuance of common stock	—	(6,250)	(6,250)
Change in fair value	25,574	7,815	33,389
Balance at December 31, 2021	$ —	$ 4,371	$ 4,371
Change in fair value	—	(1,486)	(1,486)
Balance at December 31, 2022	$ —	$ 2,885	$ 2,885

6. Accrued expenses

Accrued expenses consist of the following:

(in thousands)	December 31, 2022	December 31, 2021
Employee compensation and related benefits	$ 9,124	$ 6,050
Accrued external research and development expenses	8,919	5,041
Professional fees	1,193	1,109
License and milestone payments	310	
Other	1,221	792
Total	$ 20,767	$ 12,992

7. Leases

The Company's operating lease activity is comprised of non-cancelable facility leases for office and laboratory space in Boston, Massachusetts.

The Company has also entered into multiple contract research and contract manufacturing service agreements with third parties which contain embedded leases within the scope of ASC 842. The embedded leases are considered short term leases, as the contractual terms are twelve months or less. Accordingly, no lease liability or ROU asset has been recorded.

The components of operating lease cost were as follows:

(in thousands)	December 31, 2022	December 31, 2021
Operating lease costs	$ 5,946	$ 1,923
Variable lease costs	1,601	747
Short term lease costs	698	2,278
Total	$ 8,245	$ 4,948

Supplemental cash flow information related to operating leases was as follows:

(in thousands)	December 31, 2022	December 31, 2021
Cash paid for amounts included in the measurements of lease liabilities:		
Operating cash flows related to operating leases	$ 5,050	$ 2,021

As of December 31, 2022, the Company's operating leases were measured using a weighted-average incremental borrowing rate of 7.89% over a weighted-average remaining lease term of 10 years.

On August 19, 2021, the Company entered into a lease agreement with ARE-MA Region No. 87 Tenant, LLC, a Delaware limited liability company (the "Landlord"), pursuant to which the Company leased approximately 104,933 square feet of office and laboratory space located at 201 Brookline Avenue, Boston, Massachusetts (the "Boston Lease"), further amended in January 2022 to include an additional 249 square feet, for a total of 105,182

square feet (the “Premises”). In June 2022, the Company entered into a second amendment to specify separate target commencement dates for certain areas of the Premises.

The Premises were first made available to the Company in August 2022. Upon commencement of the lease, the Company recorded an operating lease ROU asset of $91.8 million and a total lease liability of $80.8 million.

The Company’s obligation for the payment of base rent for the Premises began in January 2023 (the “Rent Commencement Date”). Base rent is initially $0.8 million per month, and will increase by approximately 3% per annum.

The Boston Lease has a term of 10 years, measured from the Rent Commencement Date. The Company has the option to extend the term of the Boston Lease for a period of an additional five years. Under the terms of the Boston Lease, the Landlord made $21.0 million in certain tenant improvements to the Premises to suit the Company’s use (the “Tenant Improvement Allowance”), which amount is included in the base rent set forth in the Boston Lease.

In connection with its entry into the Boston Lease and as a security deposit, the Company has provided the Landlord a letter of credit in the amount of approximately $4.8 million, which may be reduced to approximately $3.5 million on the expiration of the 36-month anniversary of the Rent Commencement Date so long as there are, and have been, no defaults by the Company under the terms of the Boston Lease. The Company also paid a deposit in the amount of $0.8 million, which is equal to the first month of base rent. The Landlord has the right to terminate the Boston Lease upon customary events of default.

In July 2022 the Company notified its landlord under its prior lease of its intent to terminate that lease prior to the expiration of the term lease. As of December 31, 2022, there was no remaining ROU and lease liability for the prior lease.

In October 2021, the Company entered into a sublease for 11,931 square feet of office and laboratory space in Cambridge, Massachusetts. The sublease commenced in December 2021 and has an initial noncancelable term of 12 months. The Company had the option to extend the sublease for one extension term of three months by written notice not less than six months prior to the expiration of the sublease term. The Company did not exercise this option. Therefore, this sublease is treated as a short-term lease. The total fixed lease payments over the sublease term were approximately $1.4 million and the Company was also required to pay its proportional share of operating expenses.

Future minimum commitments under non-cancellable leases as of December 31, 2022 were as follows:

Years ending December 31,		Amount
		(in thousands)
2023	$	12,306
2024		10,563
2025		10,868
2026		11,183
2027		11,506
Thereafter		62,736
Total lease payments	$	119,162
Less: interest		(37,245)
Present value of operating lease liabilities	$	81,917

8. License agreements

Harvard/Broad license agreement and Broad license agreement

In March 2019, the Company simultaneously entered into the Harvard/Broad License Agreement and Broad License Agreement (the “license agreements”) for certain base editing technologies pursuant to which the Company received exclusive, worldwide, sublicensable, royalty-bearing licenses under specified patent rights to develop and commercialize licensed products and nonexclusive, worldwide, sublicensable, royalty-bearing licenses under certain patent rights to research and develop licensed products. The Company agreed to use commercially reasonable efforts to develop licensed products in accordance with the development plans, to introduce any licensed products that gain regulatory approval into the commercial market, to market licensed products that have gained regulatory approval following such introduction into the market, and to make licensed

products that have gained regulatory approval reasonably available to the public. The term of the agreements will continue until the expiration of the last to expire valid claim. The Company may terminate either of the license agreements without cause upon four months' prior written notice to Harvard and Broad, unless terminated earlier. In February 2021, the Company provided written notice to Broad of its intent to terminate the Broad License Agreement, which termination was effective in June 2021.

As partial consideration for the rights granted under the Harvard/ Broad License Agreement and Broad License Agreement, the Company paid $0.3 million in non-refundable upfront license fees and also issued 276,075 shares of its common stock with a fair value of $0.3 million. Additional consideration under the license agreements is as follows:

Antidilution Rights—The initial shares of common stock issued to Harvard and Broad were subject to antidilution provisions. The antidilution rights associated with the Company achieving a defined aggregate level of preferred stock financing were partially satisfied in 2019 and fully satisfied in 2020, which settlement amounts totaled $0.1 million and $0.5 million, respectively, and which amounts were settled through issuances of 121,411 and 187,867 shares of common stock, respectively. The remaining antidilution rights obligation was fully satisfied in June 2021 upon the Company's IPO. The settlement amount totaled $32.5 million and was settled through issuance of 878,098 shares of the Company's common stock.

Success Payments—The Company is required to make success payments under the license agreements as further described in Note 5, Fair value of financial instruments. In September 2021, certain success payments were triggered and amounts due to Harvard and Broad totaled $6.3 million. These amounts were settled in cash in November 2021.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, contract research organizations, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. The Company has not incurred any material costs as a result of such indemnifications and is not currently aware of any indemnification claims.

Other Payments—The Company agreed to pay an annual license maintenance fee ranging from low-to-mid five figures to low six figures, depending on the particular calendar year, for each of the license agreements. The Company is responsible for the payment of certain patent prosecution and maintenance costs incurred by Harvard and Broad related to licensed patents. To the extent achieved, the Company is obligated to pay up to an aggregate of $46.2 million and $108 million in development and sales-based milestones, respectively. In 2022, the first milestone was triggered and amounts due to Harvard and Broad totaled $0.3 million. These amounts remain payable as of December 31, 2022 and will be settled in cash. If the Company undergoes a change of control during the term of the license agreements, then certain of the milestone payments would be increased by a mid-double-digit percentage. To the extent there are sales of a licensed product, the Company is required to pay low single digit royalties on net sales, for each of the license agreements. The Company is entitled to certain reductions and offsets on these royalties with respect to a licensed product in a given country.

Beam license agreement

In April 2019, the Company and Beam Therapeutics, Inc. ("Beam") entered into a collaboration and license agreement. Pursuant to the Beam Agreement, the Company received an exclusive, worldwide, sublicensable license under certain of Beam's base editing technology, gene editing, and delivery technologies to develop, make, use, offer for sale, sell and import base editing products and nuclease products using Beam's CRISPR associated protein 12b, or Cas12b technology, in each case, directed to any of four initial gene targets, including the PCSK9 and ANGPTL3 genes, that are associated with an increased risk of coronary diseases. In addition, the Company granted Beam an exclusive, worldwide, sublicensable license under certain of its delivery technology to develop, manufacture, sell and import product candidates and products, except for base editor products licensed to Verve.

Both parties may conduct certain activities in accordance with an agreed-upon research and/or development plan. Following the dosing of a final patient in a Phase 1b clinical trial of a given licensed product for the initial gene

targets, Beam has the right to opt in to share 33% of worldwide expenses of the development of such licensed product, as well as jointly commercialize and share profits and expenses of commercializing such licensed product in the United States on a 50/50 basis. If Beam exercises its opt-in right for a given licensed product for the initial gene targets, which we refer to following such opt-in as a collaboration product, it will be obligated to pay for a specified percentage of the development and commercialization costs of such collaboration product and will have the right to receive a specified percentage of the profits from any sales of such collaboration product. The term of the Beam Agreement continues until the last to expire of any royalty term for any product. The Company has the right to terminate the Beam Agreement as to any licensed product, but not for any collaboration product, by delivering a 90-day termination notice to Beam, provided that Beam has elected not to exercise its opt-in right or the period to exercise such opt-in right has expired.

The Company is responsible for all costs and expenses incurred in the conduct of activities under the research plan, any development plan and any costs and expenses for the development of a licensed product for which Beam has not elected to opt-in.

As partial consideration for the license rights granted by Beam under the Beam Agreement, the Company paid a one-time, nonrefundable fee through issuing 276,075 shares of its common stock with a fair value of $0.3 million. To the extent achieved, for each licensed product, the Company is also obligated to pay up to $11.3 million in development and regulatory-based milestones and $15.0 million in sales-based milestones. To the extent there are sales of a licensed product, the Company is required to pay low-to-mid single digit royalties on net sales. To the extent achieved, for each collaboration product outside of the United States, the Company is obligated to pay up to $5.6 million in development and regulatory-based milestones and $7.5 million in sales-based milestones. To the extent there are ex-U.S. sales of a collaboration product, the Company is required to pay low-to-mid single digit royalties on net sales. Due to the submission of the Company's clinical trial application in New Zealand, a milestone payment of $0.3 million was triggered in 2022 and subsequently paid by the Company to Beam. Additionally, due to the first patient dosing with VERVE-101 in a clinical trial, a milestone payment of $0.2 million was triggered and paid by the Company to Beam.

The parties have also promised that in further consideration for the licenses granted under the parties' respective delivery technologies, each party will pay to the other party development-based milestone payments up to $6.0 million for each delivery technology product of such paying party to achieve the corresponding milestone event. The triggering of these milestone payments was not considered probable as of the transaction date, and no expense has been recorded for these milestones as of December 31, 2022.

On July 5, 2022, the Company entered into an Amended and Restated Collaboration and License Agreement with Beam (the "Amended Beam Agreement").

Pursuant to the Amended Beam Agreement, Beam granted the Company an exclusive, worldwide, sublicensable license under certain of Beam's base editing technology to develop and commercialize products directed towards an additional liver-mediated, cardiovascular disease target. The Company is responsible for the development and commercialization of products targeting the additional gene target, subject to Beam's opt-in right. Following the dosing of the final patient in a Phase 1b clinical trial of a licensed product for such additional gene target, Beam has the right to opt-in to share 35% of worldwide expenses of the development of such licensed product, as well as jointly commercialize and share 35% of the profits and expenses of commercializing such licensed product worldwide. If Beam does not elect to opt-in, Beam is entitled to receive milestones and royalties on the same basis as other collaboration products as provided in the Beam Agreement.

In exchange, the Company granted to Beam an exclusive, worldwide, sublicensable, fully paid-up license under the Company's intellectual property, including under the Company's GalNAc-LNP delivery technology, relating to a preclinical program developed by the Company.

The Amended Beam Agreement also clarified intellectual property rights with respect to the Company's GalNAc-LNP delivery technology; grants Beam, on a target-by-target basis, the option to obtain a non-exclusive, worldwide, sublicensable license to the Company's GalNAc-LNP delivery technology for the development and commercialization of certain base editor products, as to which Beam would owe the Company a fee upon exercise of each option, certain regulatory and commercial sale milestones as well as low single-digit royalties on net sales for base editor products using the GalNAc-LNP delivery technology; terminates the Company's rights and economic obligations under the Beam Agreement with respect to the undisclosed genes, allowing the Company and Beam to independently develop and commercialize products directed to such gene targets; and concludes other licenses that applied under the Beam Agreement with respect to delivery and other technologies developed by the parties for the development and commercialization of base editor products.

To the extent there are sales of a delivery technology product, each party will pay the other party low-to-mid single digit royalties based on the annual aggregate worldwide net sales resulting from the sale of each delivery technology product of such paying party; provided, however, that such royalty payments will not apply to net sales of the collaboration products or licensed products. The Company concluded the receipt of any milestone or royalty payments under the Amended Beam Agreement was not probable as of December 31, 2022.

Acuitas agreements

Development and option agreement

In December 2019, the Company and Acuitas Therapeutics, Inc. ("Acuitas") entered into a development and collaboration agreement, which agreement was amended and restated in October 2020. The Company agreed to reimburse Acuitas on a quarterly basis for its services performed related to the program activities based on an agreed upon number of fulltime employees committed to work on the program at an annual rate per employee, including reimbursement of reasonable external costs. The Company recognized research and development expense of approximately $0.1 million during the year ended December 31, 2022, and $1.0 million for the year ended December 31, 2021, respectively, related to the reimbursement of research and development services provided by Acuitas and technology maintenance fees. Under the terms of the agreement, the Company allowed the development and option agreement to terminate upon reaching the third anniversary of the agreement in December 2022.

License agreement

In October 2020, the Company paid Acuitas a non-refundable, upfront license fee of $2.0 million (less a previously paid target reservation fee) to exercise an option with respect to a licensed product and a licensed genome target and entered into a non-exclusive, worldwide license with Acuitas, with a right to sub-license through multiple tiers, under the licensed LNP technology to research, develop and commercialize the licensed products using the LNP technology in connection with the PCSK9 gene target for all human therapeutic or prophylactic uses.

To the extent achieved, the Company is also obligated to pay up to an aggregate of $9.8 million in clinical and regulatory milestones and $9.5 million in sales-based milestones. Due to the first patient dosing of VERVE-101 in a clinical trial, a milestone payment of $0.8 million was triggered and paid during the year ended December 31, 2022.

Novartis license agreement

In October 2021, the Company entered into a license agreement with Novartis Pharma AG (“Novartis”) to obtain a non-exclusive license to lipid technology the Company is using in connection with the research and development of certain product candidates, including VERVE-201. As consideration for the license and rights granted under the agreement, the Company made a one-time, non-refundable, upfront payment of $0.8 million during the year ended December 31, 2021. The license agreement requires the Company to pay up to an aggregate of $10.0 million in clinical and regulatory milestones and $35.0 million in sales-based milestones for products that incorporate the licensed lipid technology. The milestones have not been achieved and no expense has been recorded for these milestones as of December 31, 2022.

In June 2022, the Company amended the agreement to include three additional licensed products to the scope of the non-exclusive license. In consideration of the additional licensed products, the Company was required to make a one-time, non-refundable upfront payment of $2.8 million to Novartis. This amount was recorded as research and development expense and was paid during the year ended December 31, 2022.

9. Collaboration and License Agreements

Vertex Agreement

Summary of Agreement

In July 2022, the Company entered into the Strategic Collaboration and License Agreement (the "Vertex Agreement") with Vertex Pharmaceuticals Incorporated ("Vertex") for an exclusive, four-year worldwide research collaboration focused on developing *in vivo* gene editing candidates toward an undisclosed target for the treatment of a single liver disease. Additionally, the Company entered into a stock purchase agreement (the "Stock Purchase Agreement") with Vertex, pursuant to which the Company sold 1,519,756 shares of its common stock to Vertex at a price of $23.03 per share, for an aggregate purchase price of $35.0 million.

Pursuant to the Vertex Agreement, the Company is responsible for discovery, research and certain preclinical development of novel *in vivo* gene editing development candidates for the target of interest. The Company's research activities are focused on (i) identifying and engineering specific gene editing systems and *in vivo* delivery systems directed to the target and (ii) evaluating and optimizing development candidates to achieve criteria specified in the Vertex Agreement. Vertex is obligated to reimburse the Company's research expenses consistent with a mutually agreed-upon research plan and budget ("Research Plan"). The research term has an initial term of four years and may be extended by Vertex for up to one additional year ("Research Term"). The Research Plan is overseen by a Joint Research Committee ("JRC") as detailed in the Vertex Agreement. Any material amendments to the Research Plan are required to be mutually agreed to by the JRC.

During the Research Term, Vertex may select certain gene editing systems and *in vivo* delivery systems directed at the target to become a licensed agent. Upon the designation of the licensed agent, Vertex shall receive a license to exploit the licensed agent, and the licensed agent will continue to be developed under the Research Plan in order to achieve certain development candidate criteria agreed to by the JRC. Following the Research Term, Vertex will be solely responsible for subsequent development, manufacturing and commercialization of any product candidate resulting from the licensed agent.

The Company received an upfront payment from Vertex of $25 million and is eligible to receive (i) success payments of up to $22 million for each product candidate (up to a maximum of $66 million) that achieves the applicable development criteria, (ii) up to an aggregate of $175 million in development milestones and (iii) up to an aggregate of $165 million in commercial milestone payments. The Company is also eligible to receive tiered single-digit royalties on net sales, with the rate dependent upon the type of product and subject to specified reductions. Such royalty payments will terminate on a country-by-country and product-by-product basis upon the later to occur of (i) the expiration of the last to expire valid claim under the patent rights covering such product in such country, (ii) the period of regulatory exclusivity associated with such product in such country or (iii) ten years after the first commercial sale of such product in such country.

Prior to the first patient dosing of the first Phase 1b clinical trial for the first product candidate developed under the Vertex Agreement, the Company also has the right to opt-in to a profit share arrangement pursuant to which Vertex and the Company would share the costs and net profits for all product candidates emerging from the collaboration. If the Company exercises its opt-in right, in lieu of milestones and royalties, it will be obligated to pay for a specified percentage of the development and commercialization costs, and it will have the right to receive a specified percentage of the profits from any sales of any product candidates advanced under the collaboration. At the time the Company exercises the option, it may elect a profit/cost share of up to 40% (with Vertex retaining a minimum of 60%). In order to exercise its opt-in right, the Company is required to pay a fee ranging from $25 million to $70 million, depending on the profit/cost percentage elected by the Company and the Company's licensed technology included in the most advanced product candidate at the time it exercises its opt-in right. Under all profit share scenarios, Vertex will control the worldwide development and commercialization of any product candidates resulting from the collaboration.

The Vertex Agreement includes customary representations and warranties, covenants and indemnification obligations for a transaction of this nature. The Company and Vertex each have the right to terminate the agreement for material breach by, or insolvency of, the other party following notice, and if applicable, a cure period. Vertex may also terminate the Vertex Agreement in its entirety for convenience upon 90 days' notice.

The Company assessed the promised goods and services under the Vertex Agreement, in accordance with ASC 606. At inception, the Vertex Agreement included the following performance obligations: (i) the research services obligation which relates to the research and development services to be provided under the Research Plan (the

"Research Services") and (ii) three licensed agent material rights related to the options to obtain licenses to exploit a licensed agent, at a discount.

The Company identified $20.0 million of fixed transaction price consisting of the $25.0 million upfront fee offset by a discount of $5.0 million related to the 1,519,756 shares sold to Vertex under the Stock Purchase Agreement when measured at fair value on the date of issuance. The Company is also entitled to reimbursement of costs incurred associated with the delivery of services under the Research Plan. The Company utilized the most likely amount approach and estimated the expected cost reimbursement to be $5.8 million at inception. The Company concluded that these amounts do not require a constraint and are included in the transaction price at inception. The Company considers this estimate at each reporting date and updates the estimate based on information available. As of December 31, 2022, the estimate of the expected reimbursement is $5.8 million based on expectations as of such date. Additional consideration to be paid to the Company upon reaching certain milestones are excluded from the transaction price as that consideration may only be earned subsequent to an option exercise.

The Company has concluded that the variable consideration related to the cost reimbursement of the Research Services obligation will be allocated entirely to that obligation as the cost reimbursement relates specifically to the services being performed under the Research Plan. The reimbursement of Research Services is considered to be at a market rate and therefore depicts the estimated amount it would expect to receive for this obligation. As a result, the Company allocated the fixed consideration of $20.0 million to the three licensed agent material rights based on their relative standalone selling prices. The estimated standalone selling price for each material right was based on an adjusted market assessment approach. The Company concluded that the market would be willing to pay an equal amount for each licensed agent license on a standalone basis before being adjusted for the probability of the option becoming exercisable upon the successful completion of research activities to identify the licensed agents. The Company reached this conclusion after considering (i) the downstream economics including success fees, milestones and royalties related to each licensed agent being identical and (ii) that all licensed agents are targeting the same gene. As such, based on the relative standalone selling price for each of the three material rights, the allocation of the transaction price to the separate performance obligations is as follows:

Performance obligation		Amount (in thousands)
Research services obligation	$	5,845
First licensed agent material right		6,667
Second licensed agent material right		6,667
Third licensed agent material right		6,666
Total	$	25,845

The amount allocated to the Research Services obligation will be recognized on a proportional performance basis over the period of service using input-based measurements of total cost of research incurred to estimate the proportion performed and remeasured at the end of each reporting period. The amount allocated to the licensed agent material rights was recorded as deferred revenue and will commence recognition upon exercise of each option or, if an option is never exercised, it will be recognized in full upon expiry of the Research Term.

During the year ended December 31, 2022, the Company recognized $1.9 million of revenue associated with the Vertex Agreement related to research services performed during the period. As of December 31, 2022, the Company has recorded $20.0 million as non-current deferred revenue.

Costs incurred relating to the Company's collaboration programs under the Vertex Agreement consist of internal and external research costs, which primarily include: salaries and benefits, and preclinical research studies. These costs are included in research and development expenses in the Company's consolidated statements of operations during the year ended December 31, 2022.

10. Preferred and common stock

The Company has issued and sold 101,170,571 Series A preferred, 7,838,461 Series A-2 preferred, and 77,163,022 Series B preferred and common stock.

In June 2021, the Company amended and restated its certificate of incorporation to authorize 5,000,000 shares of preferred stock, which shares of preferred stock are currently undesignated, and 200,000,000 shares of common stock, $0.001 par value per share.

In June 2021, the Company completed its IPO, pursuant to which the Company issued and sold 16,141,157 shares of its common stock, including 2,105,368 shares of its common stock sold pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $19.00 per share, for aggregate gross proceeds of $306.7 million. The Company received approximately $281.6 million in net proceeds, after deducting underwriting discounts and offering expenses payable by the Company.

Upon the closing of the IPO, all outstanding shares of the Company's preferred stock automatically converted into 27,720,923 shares of the Company's common stock, and the Company issued 878,098 shares of its common stock to Harvard and Broad as final settlement of its antidilution rights obligation.

In July 2022, in connection with the execution of the Vertex Agreement, the Company and Vertex also entered into the Stock Purchase Agreement for the sale and issuance of 1,519,756 shares of the Company's common stock to Vertex at a price of $23.03 per share, for an aggregate purchase price of $35.0 million.

In July 2022, the Company completed a follow-on public offering of common stock, pursuant to which the Company issued and sold 9,583,334 shares of its common stock, including 1,250,000 shares of its common stock sold pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $27.00 per share. The Company received net proceeds of approximately $242.9 million after deducting underwriting discounts and offering expenses of approximately $15.8 million.

In July 2022, the Company entered into an Open Market Sale Agreement (the "Sales Agreement") with Jefferies LLC ("Jefferies") as the agent pursuant to which the Company is entitled to offer and sell, from time to time at prevailing market prices, shares of the Company's common stock. The Company agreed to pay Jefferies a commission of up to 3.0% of the aggregate gross sale proceeds of any shares sold by Jefferies under the Sales Agreement. During the year ended December 31, 2022, the Company sold 1,280,168 shares of its common stock under the Sales Agreement for aggregate net proceeds of $42.9 million, after deducting commissions and offering expenses payable by the Company.

The holders of common stock are entitled to one vote for each share of common stock.

11. Stock-based compensation

The 2018 Equity Incentive Plan (the "2018 Plan"), adopted by the board of directors in August 2018 provided for the grant of qualified incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock and restricted stock units to the Company's employees, officers, directors, advisors, and outside consultants for the issuance or purchase of shares of the Company's common stock. The maximum number of shares of common stock that were authorized for issuance under the 2018 Plan was 6,885,653.

In June 2021, the Company's board of directors adopted, and the Company's stockholders approved, the 2021 Stock Incentive Plan (the "2021 Plan"), which became effective on June 16, 2021. The 2021 Plan provides for grant of qualified and nonqualified stock options, stock appreciation rights, restricted and unrestricted stock and stock units, performance awards, and other share-based awards to the Company's employees, directors, advisors and outside consultants. The shares reserved for issuance pursuant to the 2021 Plan are subject to an annual increase through January 1, 2031. As of December 31, 2022 the Company had reserved 7,057,629 shares of the Company's common stock for issuance of stock options, restricted stock, and restricted stock units, of which 3,025,807 remained outstanding for future grant under the 2021 Plan. On January 1, 2023, 3,086,541 shares of the Company's common stock were added to the amount reserved for issuance under the 2021 Plan. Upon effectiveness of the 2021 Plan, the Company ceased granting additional awards under the 2018 Plan.

Stock-based compensation expense recorded in the consolidated statements of operations and comprehensive loss is as follows:

	Year ended December 31,		
(in thousands)	**2022**	**2021**	**2020**
Research and development	$ 12,486	$ 3,830	$ 494
General and administrative	9,991	3,242	356
Total stock-based compensation expense	$ 22,477	$ 7,072	$ 850

Stock options

The assumptions used in Black-Scholes for stock options granted were as follows:

	Year ended December 31,		
	2022	2021	2020
Expected volatility	77.3%	77.7%	84.8%
Weighted-average risk-free interest rate	2.4%	0.9%	0.4%
Expected dividend yield	—	—	—
Expected term (in years)	6.0	6.0	6.0

The following table provides a summary of stock option activity during the year ended December 31, 2022:

	Number of options	Weighted average exercise price per share	Weighted average remaining contractual life (in years)	Aggregate intrinsic value[2] (in thousands)
Outstanding at December 31, 2021	6,119,295	$ 9.44		
Granted	2,561,300	$ 28.49		
Exercised	(743,638)	$ 2.92		
Forfeited	(324,131)	$ 20.37		
Outstanding at December 31, 2022	7,612,826	$ 16.10	8.3	$ 63,790
Exercisable at December 31, 2022	2,551,841	$ 7.52	7.6	$ 34,295
Expected to vest after December 31, 2022[1]	5,060,985	$ 20.43	8.6	$ 29,495

(1) This represents the number of unvested options outstanding as of December 31, 2022 that are expected to vest in the future.
(2) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the estimated fair value of the common stock for the options that were in the money as of December 31, 2022.

During the year ended December 31, 2022 the weighted average grant date fair value of the stock options granted was $19.39 per share. The aggregate intrinsic value of stock options exercised during the year ended December 31, 2022 was approximately $21.2 million while the Company received $2.2 million in proceeds for the exercise of these options.

As of December 31, 2022, there was $64.4 million of unrecognized compensation cost related to unvested stock options, which is expected to be recognized over a weighted-average period of approximately 2.5 years.

Restricted stock and restricted stock units

In 2018, the Company issued 2,150,537 shares of restricted common stock. The restricted shares vested in 48 equal monthly installments, commencing on January 1, 2018. The restricted shares were fully vested as of December 31, 2021.

During the year ended December 31, 2022, the Company granted 688,700 restricted stock units under the 2021 Plan. These restricted stock units vest in substantially equal installments over a four-year period.

A summary of the status of and change in unvested restricted stock units as of December 31, 2022 was as follows:

	Shares	Weighted-average grant date fair value per share
Unvested restricted stock units as of December 31, 2021	32,000	$ 36.58
Restricted stock units granted	688,700	$ 22.65
Restricted stock units vested	(6,375)	$ 35.53
Restricted stock units forfeited	(36,500)	$ 24.32
Unvested restricted stock units as of December 31, 2022	677,825	$ 23.10

At December 31, 2022, there was $13.6 million of unrecognized stock-based compensation expense related to restricted stock units that are expected to vest. These costs are expected to be recognized over a weighted-average remaining vesting period of 3.5 years.

2021 Amended and Restated Employee Stock Purchase Plan

In June 2021, the board of directors adopted, and the Company's stockholders approved, the 2021 Employee Stock Purchase Plan, or the ESPP, as amended and restated, which became effective on June 16, 2021. The shares reserved for issuance pursuant to the ESPP are subject to an annual increase through January 1, 2031. As of December 31, 2022, 134,107 shares had been purchased by employees under the ESPP and 784,326 shares remained available for issuance under the ESPP. On January 1, 2023, 617,308 shares of common stock were added to the amount reserved for sale under the ESPP.

12. Net loss per share attributable to common stockholders

The following table summarizes the computation of basic and diluted net loss per share attributable to common stockholders of the Company:

	Year ended December 31,		
(in thousands, except share and per share amounts)	**2022**	**2021**	**2020**
Numerator:			
Net loss attributable to common stockholders	$ (157,387)	$ (120,314)	$ (45,704)
Denominator:			
Weighted average number of common shares, basic and diluted	54,023,653	26,872,036	2,250,093
Net loss per common share attributable to common stockholders, basic and diluted	$ (2.91)	$ (4.48)	$ (20.31)

The Company's potential dilutive securities, which include convertible preferred stock, unvested restricted stock, unvested restricted stock units, and common stock options, have been excluded from the computation of diluted net loss per share as the effects would be anti-dilutive. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares, presented based on amounts outstanding at period end, from the computation of diluted net loss per share attributable to common stockholders for the period indicated because including them would have had an anti-dilutive effect:

	Year ended December 31,		
	2022	**2021**	**2020**
Convertible preferred stock	—	—	19,387,544
Unvested restricted stock	—	—	537,633
Unvested restricted stock units	677,825	32,000	—
Outstanding options to purchase common stock	7,612,826	6,119,295	3,888,823
Total	8,290,651	6,151,295	23,814,000

As part of the license agreements with Harvard and Broad, the Company is required to make success payments. The Company may elect to make these payments by issuing shares of the Company's common stock. As of December 31, 2022, an aggregate of $6.3 million was earned relating to these success payments, which the Company settled in cash in November 2021. No success payments were triggered or paid during the year ended December 31, 2022.

13. Income taxes

The Company's losses before income taxes consist solely of losses from domestic operations, which totaled $157.4 million, $120.3 million and $45.7 million for the years ended December 31, 2022, 2021, and 2020, respectively.

Income tax expense (benefit) is summarized as follows:

(in thousands)	Year ended December 31, 2022	2021	2020
Current:			
Federal	$ -	$ -	$ -
State	53	-	-
Foreign	-	-	-
Total current provision	$ 53	$ -	$ -
Deferred:			
Federal	-	-	-
State	-	-	-
Foreign	-	-	-
Total deferred provision	$ -	$ -	$ -

A reconciliation of the income tax expense computed using the federal statutory income tax rate to the Company's effective income tax rate is as follows:

(in thousands)	Year ended December 31, 2022	2021	2020
Federal statutory rate	21.0%	21.0%	21.0%
Change in valuation allowance	(34.7)%	(31.3)%	(29.6)%
Stock-based compensation	(0.3)%	0.9%	(0.3)%
Executive compensation	(0.8)%	(1.1)%	0.0%
Permanent items	(0.2)%	(0.1)%	1.1%
State income taxes, net of federal benefit	8.4%	6.1%	6.8%
Research and development tax credits	5.6%	4.5%	1.0%
Other	1.0%	0.0%	0.0%
Effective income tax 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 and liabilities as of December 31, 2022 and 2021 are comprised of the following:

	December 31,	
(in thousands)	**2022**	**2021**
Deferred tax assets:		
Net operating loss carryforwards	$ 43,779	$ 33,409
Capitalized costs—net of amortization	11,095	12,395
Research and development tax credits	20,835	6,098
Capitalized research costs	28,650	—
Stock-based compensation	3,669	1,117
Other	174	76
Lease liability	22,285	533
Accrued expenses	5,024	2,852
Total deferred tax assets	135,511	56,480
Deferred tax liabilities:		
Property and equipment	(881)	(899)
Right of use asset	(24,994)	(501)
Total deferred tax liabilities	(25,875)	(1,400)
Total deferred tax assets, net	109,636	55,080
Less: valuation allowance	(109,636)	(55,080)
Deferred tax assets, net of valuation allowance	$ —	$ —

The Company has incurred net operating losses in each year since inception. Management has evaluated the positive and negative evidence bearing upon the realizability of the Company's net deferred tax assets, which are comprised primarily of net operating loss carryforwards, tax credits, and costs capitalized for tax purposes. Management has considered the Company's history of cumulative net losses in the United States and estimated future tax losses and has determined that it is more likely than not that the Company will not recognize the benefits of the net deferred tax assets. As a result, the Company has recorded a full valuation allowance at December 31, 2022 and 2021. The valuation allowance increased by $54.6 million in 2022, due to the increase in deferred tax assets, primarily due to net operating loss carryforwards, tax credit carryforwards, and increase in deferred tax assets associated with current year temporary items.

Realization of the future tax benefits is dependent on many factors, including the Company's ability to generate taxable income within the net operating loss carryforward period. The Company's ability to utilize these federal and state net operating loss and research and development credit carryforwards may be limited in the future if the Company experiences an ownership change pursuant to Internal Revenue Code 382. An ownership change occurs when the ownership percentages of 5% or greater shareholders change by more than 50% over a three-year period. As of December 31, 2022, the Company has not completed a study to assess whether a change of control has occurred and whether the net operating losses and credits are limited due to a change in ownership. To the extent that an assessment is completed in the future, the Company's ability to utilize tax attributes could be restricted on a year-by-year basis and certain attributes could expire before they are utilized.

As of December 31, 2022, the Company had approximately $163.9 million of federal and $148.0 million of state net operating loss carryforwards The federal net operating losses have an indefinite life and can be utilized to offset 80% of future taxable income, while the state net operating losses will start to expire at various dates through 2042. Additionally, as of December 31, 2022, the Company had approximately $14.4 million of federal and $8.2 million of Massachusetts tax research and development credits that expire starting in 2042 and 2037, respectively.

As of December 31, 2022 and 2021, the Company had no uncertain tax positions. The Company recognizes both interest and penalties associated with unrecognized tax benefits as a component of income tax expense. The Company has not recorded any interest or penalties for unrecognized tax benefits since its inception.

The Company files income tax returns in the United States, California, Connecticut, the Commonwealth of Massachusetts, Pennsylvania, and Wisconsin. The Company is not currently under examination by the Internal Revenue Service or any other jurisdiction. All tax years remain open to tax examination. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period.

14. Related party transactions

An executive officer of Beam was a board member of the Company until August 2022.

In October 2020, the Company and Beam entered into a materials exchange agreement wherein the parties agreed that Beam would provide certain mRNA, gRNA, and protein to the Company and that the Company would provide certain gRNAs to Beam at an agreed upon price per each material provided. For the years ended December 31, 2022 and 2021, respectively, the Company recognized $0.4 million and $0.2 million as a reduction to research and development expense related to reimbursements received for materials sold to Beam.

In December 2021, the Company entered into a sublease agreement with Beam for laboratory and office space in Cambridge, Massachusetts, which sublease terminated in December 31, 2022. Total rent payments under this sublease were $1.8 million for the year ended December 31, 2022.

An executive of Broad was a board member of the Company. The board member resigned, effective May 2021. In March 2019, the Company simultaneously entered into the Harvard/Broad License Agreement and Broad License Agreement for certain base editing technologies pursuant to which the Company received exclusive, worldwide, sublicensable, royalty-bearing licenses under specified patent rights to develop and commercialize licensed products and nonexclusive, worldwide, sublicensable, royalty-bearing licenses under certain patent rights to research and develop licensed products. Additional consideration under the license agreements include antidilution rights and success payments. See Note 8, License agreements.

15. Employee benefit plans

The Company has a defined-contribution plan established under Section 401(k) of the Internal Revenue Code (the “401(k) Plan”), which covers substantially all employees. Employees are eligible to participate in the 401(k) Plan beginning on the first day of employment. The 401(k) Plan includes a salary deferral arrangement pursuant to which participants may elect to reduce their current compensation by up to the statutorily prescribed limit, equal to $20,500 in 2022 with a catch up contribution limit equal to $6,500 for those 50 years of age or older, and have the amount of the reduction contributed to the 401(k) Plan. Since January 1, 2020 the Company matches 100% of each participant’s annual contribution to the 401(k) plan up to 3% of the participant’s salary and then 50% of each participant’s contribution up to 2% of the participant’s salary. The match immediately vests 100%. The matching contributions by the Company to the 401(k) plan were $1.0 million, $0.4 million, and $0.1 million for the years ended December 31, 2022, 2021, and 2020, respectively.

16. Subsequent events

The Company evaluated all subsequent events and determined there are no material recognized or unrecognized subsequent events requiring disclosure.

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Management Team

Sekar Kathiresan, M.D.
Co-Founder and Chief Executive Officer

Andrew Ashe, J.D.
President, Chief Operating Officer and General Counsel

Andrew Bellinger, M.D., Ph.D.
Chief Scientific Officer and Chief Medical Officer

Allison Dorval
Chief Financial Officer

Joan Nickerson
Chief Administrative Officer

Legal Counsel

Wilmer Cutler Pickering Hale and Dorr LLP
Boston, MA

Independent Auditors

Ernst & Young LLP
Boston, MA

Transfer Agent and Registrar

Computershare Trust Company, N.A.
Louisville, KY

Board of Directors

Burt Adelman, M.D.
Chair of the Board of Directors of Verve Therapeutics, Inc.

Lonnel Coats
Chief Executive Officer and Director, Lexicon Pharmaceuticals

Bo Cumbo
President and Chief Executive Officer, Solid Biosciences

Sekar Kathiresan, M.D.
Co-Founder and Chief Executive Officer, Verve Therapeutics, Inc.

Michael MacLean
Chief Financial Officer and Chief Business Officer, Avidity Biosciences

Sheila Mikhail, J.D., MBA
Co-Founder and Former Chief Executive Officer, Asklepios BioPharmaceutical, Inc.

Krishna Yeshwant, M.D., MBA
General Partner, GV

Stock Information

Our shares of common stock are traded on the Nasdaq Global Select Market under the symbol “VERV”.

Forward-Looking Statement

This annual report contains forward-looking statements within the meaning of applicable federal securities laws and regulations. Any statements contained in this annual report that are not statements of historical fact may be deemed to be forward-looking statements, including statements regarding the timing and availability of clinical data from the Company’s heart-1 clinical trial, the timing of initiation of clinical trials of VERVE-201, the Company’s research and development plans, and the potential advantages and therapeutic potential of the Company’s programs, including VERVE-101 and VERVE-201. Without limiting the foregoing, the words “believes,” “intends,” “anticipates,” “plans,” “expects,” “seeks,” “estimates,” “would,” “should,” “likely,” “will,” “may,” “continue,” “could,” “vision,” or similar expressions are intended to identify forward-looking statements. While we may elect to update forward-looking statements in the future, we specifically disclaim any obligation to do so, even if our expectations change. A number of factors could cause our results to differ materially from those indicated by such forward-looking statements, including those detailed under the heading “Risk Factors” in Part 1, Item 1A in the accompanying Annual Report on Form10-K for the fiscal year ended December 31, 2022 and our subsequent filings with the U.S. Securities and Exchange Commission.

verve™ THERAPEUTICS

2022 ANNUAL REPORT

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NASDAQ: VERV