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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM
10-K

(Mark One)

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

For the fiscal year ended December 31, 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 001-38944

Akero Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**81-5266573**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
601 Gateway Boulevard, Suite 350 South San Francisco, CA	**94080**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code **(650) 487-6488**

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 $0.0001 per share	AKRO	The 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 Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

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

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

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was $340,434,662 as of June 30, 2022 (based on a closing price of $9.45 per share as quoted by the Nasdaq Global Select Market as of such date). In determining the market value of non-affiliate common stock, shares of the registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 14, 2023, the total number of shares outstanding of the registrant's Common Stock was 46,970,989 shares.

Documents Incorporated by Reference:

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2023 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2022. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

SUMMARY OF THE MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties, including those described in Part II, Item 1A. "Risk Factors" in this Annual Report on Form 10-K. The principal risks and uncertainties affecting our business includes:

- Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control, including difficulties in identifying patients with nonalcoholic steatohepatitis ("NASH"), significant competition for recruiting such patients in clinical trials, and restrictions on patients and investigators related to the ongoing coronavirus disease ("COVID-19") pandemic.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than us.
- Failures or delays in the commencement or completion of, or ambiguous or negative results from our planned clinical trials of our product candidates, could result in increased costs to us and could delay, prevent, or limit our ability to generate revenue and continue our business.
- Clinical development is uncertain and our clinical trials for efruxifermin ("EFX") and any future product candidates may experience delays, which would adversely affect our ability to obtain regulatory approvals or commercialize these programs on a timely basis or at all, which would have an adverse effect on our business.
- We rely and will continue to rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize any potential product candidates.
- The manufacture of our product candidates is complex and we may encounter difficulties in production. If we or any of our third-party manufacturers encounter such difficulties, or fail to meet rigorously enforced regulatory standards, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.
- We are heavily dependent on the success of EFX, our only product candidate.
- If we fail to develop and successfully commercialize other product candidates, our business and future prospects may be harmed and our business will be more vulnerable to any problems that we encounter in developing and commercializing our product candidate.
- We may develop EFX, and potentially future product candidates, in combination with other therapies, which exposes us to additional risks.
- If we are not successful in discovering, developing, receiving regulatory approval for and commercializing EFX and any future product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.
- We may be required to make significant payments under our license agreement for EFX.
- The regulatory approval processes of the U.S Food and Drug Administration (the "FDA") and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. Our inability to obtain regulatory approval for EFX or any future product candidate would substantially harm our business.
- Even if we are able to obtain regulatory approvals for our product candidate or any future product candidates, if they exhibit harmful side effects after approval, our regulatory approvals could be revoked or otherwise negatively impacted, and we could be subject to costly and damaging product liability claims.
- Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which, if violated, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.
- We have incurred significant losses since our inception and we expect to incur losses for the foreseeable future.
- We currently have a limited operating history, have not generated any revenue to date, and may never become profitable.
- We will require additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. As a result, we may not complete the development and commercialization of our product candidate or develop any future product candidates.
- Business interruptions resulting from the ongoing COVID-19 pandemic or similar public health crises, as well as from geopolitical and military conflict such as the ongoing warfare in Ukraine, could cause a disruption of the development of our product candidates and adversely impact our business.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). These statements involve risks, uncertainties, and other factors that may cause actual results, levels of activity, performance, or achievements to be materially different from the information expressed or implied by these forward-looking statements. All statements, other than statements of historical facts, 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 and expected market growth are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, among other things, statements about:

- the success, cost and timing of our product development activities and clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our research and development programs;
- our ability to successfully conduct and complete our ongoing Phase 2b clinical trial of EFX in patients with NASH who have F2 or F3 fibrosis, known as the HARMONY study, including the ability to obtain data and maintain our expected timelines during the ongoing COVID-19 pandemic;
- our ability to complete enrollment in our ongoing Phase 2b clinical trial of EFX in patients with NASH who have cirrhosis (F4 fibrosis, compensated), known as the SYMMETRY study, including the ability to obtain data and maintain our expected timelines during the ongoing COVID-19 pandemic;
- the timing and outcome of any End-of-Phase 2 meeting with FDA, or similar meetings with other regulatory authorities;
- our ability to meet all FDA requirements and the requirements of other regulatory authorities to initiate and complete Phase 3 studies of EFX in a timely manner;
- our ability to successfully conduct the ongoing expansion cohort of the SYMMETRY study, known as Cohort D, which is evaluating EFX in patients who have both Type 2 Diabetes, or T2D, and NASH, and are being treated with GLP-1 therapeutics to manage their T2D;
- the potential for COVID-19 or other pandemic, epidemic or outbreak of an infectious disease, to disrupt our business plans, product development activities, ongoing clinical trials, including the timing and enrollment of patients, the health of our employees and the strength of our supply chain;
- our ability to advance any product candidate into or successfully complete any clinical trial;
- our ability to successfully manufacture our product candidates for future clinical trials or for commercial use, if approved;
- the potential for our identified research priorities to advance our technologies;
- our ability to obtain and maintain regulatory approval, if obtained, of EFX or any future product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate;
- the ability to license additional intellectual property relating to any future product candidates and to comply with our existing license agreement;
- our ability to commercialize our products in light of the intellectual property rights of others;
- the success of competing therapies that are or become available;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- the commercialization of our product candidates, if approved;
- our plans to research, develop and commercialize our product candidates;
- our ability to attract collaborators with development, regulatory and commercialization expertise;
- future agreements with third parties in connection with the commercialization of our product candidates and any other approved product;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates, if approved;
- regulatory developments in the United States and foreign countries;

- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations; and
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates.

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 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 that we may make or into which we may enter.

You should read this Annual Report on Form 10-K and the documents that we reference herein and have filed or incorporated by reference as exhibits hereto completely and with the understanding that our actual future results may be materially different from what we expect. 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 law.

NOTE REGARDING TRADEMARKS

Akero Therapeutics, Inc. is the owner of the AKERO trademark, as well as certain other trademarks, including design versions of some of these trademarks. The symbols ™ and ® are not used in connection with the presentation of these trademarks in this report and their absence does not indicate a lack of trademark rights. Certain other trademarks used in this report are the property of third-party trademark owners and may be presented with or without trademark references.

All brand names or trademarks appearing in this report are the property of their respective owners. Unless the context requires otherwise, references in this report to "Akero," the "Company," "we," "us" and "our" refer to Akero Therapeutics, Inc. and its subsidiary.

PART I

Item 1. Business

Overview

We are a clinical-stage company dedicated to developing transformational treatments for patients with serious metabolic diseases marked by high unmet medical need, including non-alcoholic steatohepatitis, or NASH, a disease without any approved therapies. NASH is a severe form of nonalcoholic fatty liver disease, or NAFLD, characterized by inflammation and fibrosis in the liver that can progress to cirrhosis, liver failure, cancer and death. Our lead product candidate, efruxifermin, or EFX, is an analog of fibroblast growth factor 21, or FGF21, which is an endogenously expressed hormone that protects against cellular stress and regulates metabolism of lipids, carbohydrates and proteins throughout the body. Based on statistically significant fibrosis regression and NASH resolution among patients with biopsy-confirmed pre-cirrhotic NASH, as well as consistent results across multiple clinical trials, we believe EFX has the potential, if approved, to be a best-in-class medicine for treating NASH.

EFX has been evaluated in four randomized, double-blind, placebo-controlled clinical trials for which results have been reported. In these clinical trials, a total of 244 adult patients with either NASH (N=161) or T2D (N=83) were treated with EFX and evaluated for up to 24 weeks. We reported Week 24 results of the Phase 2b HARMONY study in patients with pre-cirrhotic NASH (F2-F3) fibrosis in September 2022. Both the 50mg and 28mg EFX dose groups achieved statistical significance on primary and secondary histology endpoints after 24 weeks. On the primary endpoint of at least a one-stage improvement of fibrosis without worsening of NASH, the 50mg group (41%) and 28mg group (39%) had a response rate approximately double that of placebo (20%). In addition, 76% of patients treated with 50mg EFX and 47% of those treated with 28mg achieved NASH resolution without worsening of fibrosis, which represented response rates approximately three to five times the placebo rate of 15%. We also observed 41% and 29% response rates for the 50mg and 28mg dose groups, respectively, on a combined endpoint of at least a one-stage improvement in fibrosis and NASH resolution, which were approximately six to eight times the 5% placebo rate. Significant improvements in non-invasive fibrosis markers, liver fat, liver enzymes, lipoproteins, and glycemic control were also observed for both EFX dose groups, with an additional significant reduction in body weight observed for the 50mg dose group. Across EFX groups, the most frequent adverse events were mild gastrointestinal events. We believe these results favorably differentiate EFX within the NASH landscape.

EFX is currently being evaluated in two Phase 2b clinical trials in patients with biopsy-confirmed NASH: a long-term follow-up period for the HARMONY study in patients with pre-cirrhotic NASH (F2-F3 fibrosis), for which we reported results after 24 weeks of treatment, and the SYMMETRY study in patients with cirrhotic NASH (F4 fibrosis, compensated). The SYMMETRY study includes an expansion cohort, known as Cohort D, evaluating the safety and tolerability of EFX compared to placebo when added to an existing GLP-1 receptor agonist in patients with pre-cirrhotic NASH (F1-F3 fibrosis) and Type 2 diabetes. We expect to report the results of Cohort D in the second quarter of 2023 and the results of the SYMMETRY study in the fourth quarter of 2023.

Results from the 16-week Phase 2a BALANCED study, which included an expansion cohort of patients who had cirrhosis due to NASH known as Cohort C, as well as the recent results from the 24-week HARMONY study, support our confidence that we will observe statistically significant histological improvements in the SYMMETRY main study evaluating EFX for the treatment of patients with NASH due to cirrhosis. For example, in Cohort C we observed either a one-stage improvement in fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis in 58 percent of EFX-treated patients, compared with 0% for the placebo group, after only 16 weeks of treatment. Response rates for non-invasive markers of fibrosis in Cohort C, which were comparable to the results observed for the BALANCED and HARMONY studies in patients with pre-cirrhotic NASH, are consistent with these initial histology results.

The FDA has granted both a Fast Track designation and Breakthrough Therapy designation for EFX for the treatment of NASH. In addition, the European Medicines Agency, or EMA, has granted a Priority Medicines, or PRIME, designation for EFX for the treatment of NASH. The Fast Track and PRIME programs are designed to enhance regulatory support for the development of promising investigational medicines where early clinical data suggest the potential to meet a high unmet medical need. The FDA's Breakthrough Therapy Designation is meant to expedite development and review of a therapy for a serious or life-threatening disease or condition when preliminary clinical

evidence indicates the drug may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies. Benefits of these programs may include more frequent regulatory interactions, enhanced guidance on the overall development plan and regulatory strategy, and accelerated assessment of marketing authorization, or MA, applications.

As demonstrated across four separate clinical trials in patients with NASH and/or T2D for which results have been reported, EFX has a unique ability to reproduce the actions of native FGF21. Consequently, we believe EFX holds the potential to be a highly differentiated, best-in-class FGF21 analog and promising monotherapy for the treatment of NASH, if approved. NASH is a complex disease, and its ideal treatment would include intervening at each stage of its pathogenesis. We believe EFX could potentially address all stages of NASH pathogenesis in a single treatment: reversing fibrosis, resolving steatohepatitis, and helping to restore healthy metabolism to the whole body. We also believe EFX may be able to be used in combination with other therapies for potentially greater effect in certain subpopulations, particularly among the substantial proportion of patients with both NASH and T2D who are expected to be treated with GLP-1 therapeutics to manage their T2D.

In June 2018, we acquired exclusive global development and commercialization rights to EFX from Amgen Inc., or Amgen, which leveraged its deep protein engineering expertise to design and develop EFX. As of March 6, 2023, our patent portfolio relating to EFX and other peptides included 169 issued patents and 15 pending patents worldwide, with expected patent exclusivity up to 2034 in the United States, including potential patent term extension. Since EFX is a biologic, marketing approval would also provide twelve years of market exclusivity from the approval date of a Biologics License Application, or BLA, in the United States.

Our management team has extensive experience in drug discovery, development and commercialization, and has been involved in the approvals of more than 20 medicines. Our Chief Executive Officer, Andrew Cheng, MD, PhD, was formerly Chief Medical Officer at Gilead, and responsible for clinical development for Gilead's HIV program. Our Chief Development Officer, Kitty Yale, led global clinical operations and management of Gilead's oncology, HIV, inflammation and liver disease trials. Our Chief Scientific Officer, Tim Rolph, DPhil, was formerly Chief Scientific Officer of Pfizer's Cardiovascular & Metabolic Disease Research Unit, and oversaw Pfizer's FGF21 program. We believe that our team is well positioned to leverage its collective experience in drug development and in-depth knowledge of FGF21 biology and metabolic diseases to develop and commercialize products that will have significant benefits for patients with NASH and other serious metabolic diseases with high unmet medical need.

Our Strategy

Our goal is to become a leading biotechnology company focused on developing and commercializing transformative treatments for serious metabolic diseases with high unmet medical need, with an initial focus on NASH. The key components of our strategy are to:

Advance EFX through clinical development in both pre-cirrhotic (F2/F3) and cirrhotic (F4, compensated) NASH. We believe that EFX has the potential to be a best-in-class FGF21 analog, if approved, for the treatment of NASH. Data from our Phase 2a BALANCED and Phase 2b HARMONY studies suggest that EFX has the potential to achieve industry-leading levels of fibrosis improvement as well as resolution of steatohepatitis and improvements in glycemic control and lipoprotein profile. We are committed to accelerating development as much as possible for patients with either pre-cirrhotic or cirrhotic NASH, consistent with guidance from regulatory authorities.

Scale our capabilities to support development and commercialization of EFX. We are scaling our manufacturing and organizational capabilities to capitalize on our exclusive, global rights to market EFX. We have successfully manufactured drug substance at Boehringer Ingelheim and have successfully scaled up manufacturing of a new drug product-device combination at Vetter Pharma. Drug product-device combination units have been manufactured in compliance with current good manufacturing practices, or GMP and released for use in Phase 3 clinical trials. When appropriate, we intend to develop the commercial infrastructure required for bringing EFX to patients with NASH in the United States, if approved. We also plan to evaluate options, including potential strategic collaborations, for delivering EFX, if approved, to patients in other key markets, such as Europe, Japan and China.

Leverage our knowledge of FGF21 biology to bring EFX to additional patients with metabolic diseases. Numerous publications have shown that increases in endogenous FGF21 expression occur in response to various types

of metabolic and cellular stress arising from obesity, diabetes, mitochondrial diseases and cardiovascular disease, as well as NASH. EFX has been engineered to reproduce the biological activity profile of native FGF21 while also addressing certain therapeutic limitations, such as a short half-life. We are exploring opportunities to develop EFX for additional indications where there is a compelling scientific rationale, strong clinical tractability and significant unmet medical need.

Enhance our position as a leading metabolic disease company by developing, acquiring or in-licensing additional investigational product candidates. We are continually evaluating opportunities to build a robust pipeline of potential leading treatments for serious metabolic diseases. We may select additional assets for their potential as stand-alone monotherapies or for eventual use in combination with other products.

Our Pipeline

Our pipeline is anchored by EFX, a potential best-in-class FGF21 analog for treatment of NASH, if approved. We have one EFX program focused on patients with pre-cirrhotic NASH (F2-F3), which is supported by the HARMONY study, an ongoing Phase 2b clinical trial. We have a second EFX program focused on patients with cirrhotic NASH (F4, compensated), which is supported by the SYMMETRY study, an ongoing Phase 2b clinical trial. These two programs align with FDA guidance published in 2018 and 2019, which recommends different regulatory approval pathways for patients with pre-cirrhotic and cirrhotic NASH.

Akero's Pipeline

NASH Overview

NASH is a severe form of NAFLD, which is driven by the global obesity epidemic. Patients with NAFLD have an excessive accumulation of fat in the liver resulting from an excess of caloric intake over energy needs. In patients with NASH, excessive liver fat leads to hepatocyte stress, which triggers localized inflammation and can cause extensive scarring, or fibrosis, of the liver, as the liver attempts to repair and replace damaged cells.

Patients with NASH are at increased risk of liver-related morbidity and mortality, including liver failure and hepatocellular carcinoma. As NASH progresses, cardiovascular-related morbidity and mortality also increase, with cardiovascular disease being the most frequent cause of death in patients with NASH. The prevalence of patients with advanced fibrosis (F2-F4) in the United States is projected to rise to 14.1 million by 2030, representing a roughly 100% increase from an estimated 6.7 million in 2016.

Diagnosis and disease burden

NASH is currently diagnosed through liver biopsy and its severity is measured using scoring systems that assess the extent and severity of steatosis, lobular inflammation, hepatocellular ballooning and fibrosis. Some patients may be diagnosed with NASH after presenting with symptoms such as general fatigue and nondescript abdominal

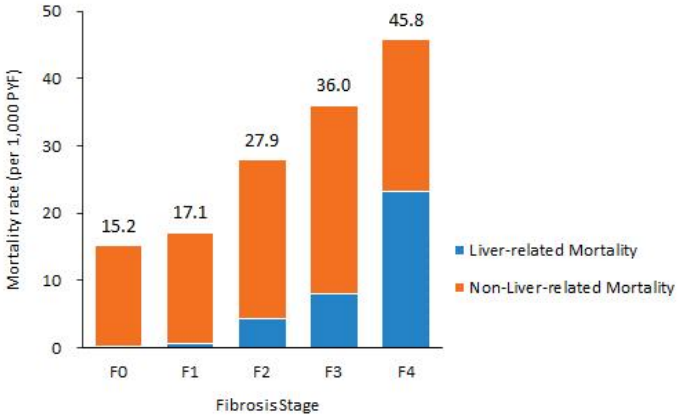
discomfort. However, NASH diagnosis more commonly follows detection of elevated liver enzymes on routine lab tests or detection of an enlarged steatotic liver by abdominal imaging. Although noninvasive methods, including a combination of imaging, such as Magnetic Resonance Imaging Protein Density Fat Fraction, or, MRI-PDFF, and fibroscan, and plasma biomarkers of fibrosis, such as Pro-C3, are being evaluated as potential diagnostic tools, none have yet been validated for use in formal NASH diagnosis.

Two different scoring systems are most commonly used in the United States to measure the severity of NASH: the NAFLD activity score, or NAS, and fibrosis stage. The NAS, which was developed for, and generally only used in, clinical trials, is a measure of liver histology that grades disease activity in patients with NAFLD and NASH. A patient may receive a composite NAS score of 0-8, which is comprised of three individual scores: (1) steatosis, scored 0-3 according to the percentage of a microscopic field showing steatosis, (2) lobular inflammation, scored 0-3 according to the number of immune cell foci per 20x optical field in a microscope, and (3) hepatocellular ballooning, scored 0-2 according to the number of ballooning cells in a microscopic field. In addition, fibrosis staging is used to classify the extent and severity of fibrosis with a scoring system based on a scale from 0-4, or F0-F4. Early, discrete fibrosis is classified as F1 or F2, whereas bridging fibrosis is classified as F3. As more hepatocytes die and scarring becomes extensive, the liver becomes cirrhotic, which is classified as stage F4.

Patients with NASH are at increased risk of liver damage and other complications. Fibrosis is generally reversible in its early-to-mid stages. However, late-stage fibrosis can be irreversible in the absence of therapy and prevents the liver from performing its natural functions.

NASH is commonly associated with metabolic comorbidities, including obesity, T2D, dyslipidemia and hypertension. In addition, the majority of patients with NASH also present with metabolic syndrome. As shown in the figure below, which is based on a pooled meta-analysis of multinational clinical trial data published in Hepatology (2017), liver-related mortality increases with fibrosis stage. As compared to healthy individuals, patients with NASH also experience higher all-cause morbidity and mortality resulting from major adverse cardiovascular events, and non-liver cancers. The most common cause of death in patients with NASH is cardiovascular disease. As with liver-related mortality, all-cause mortality also increases with fibrosis stage. Our focus is on patients with F2-F4 fibrosis, which have the highest liver-related and non-liver-related mortality rates among patients with NASH.

All-cause NASH mortality



Market size and trends

According to studies published in Hepatology (2018) and F1000Research (2018), more than one billion people worldwide were estimated to have NAFLD in 2016, including an estimated 85 million individuals in the United States. Approximately 10-20% of patients with NAFLD progress to NASH, including an estimated 17.3 million individuals in the United States and 16.4 million aggregate individuals in France, Germany, Italy, Spain, the United Kingdom, and Japan in 2016. As the population ages, the prevalence of NASH is projected to increase approximately 50% by 2030 to a total of 27.0 million individuals in the United States and 22.5 million aggregate individuals in France, Germany, Italy, Spain, the United Kingdom and Japan. However, NASH afflicts all age groups, including teenagers and young adults, for whom the loss of quality-adjusted life years will be substantial unless progression to late-stage diseases can be halted or reversed. According to a study published in Hepatology (2016), in the absence of approved therapies, direct healthcare costs associated with NAFLD and NASH in the United States were estimated to be approximately $100 billion in 2016.

Growth in prevalence of NASH in the United States is projected to be greatest in patients with stage F2-F4 fibrosis, with more than a doubling across these stages between 2016 and 2030 and higher growth rates with each advancing fibrosis stage. More than 14 million Americans are projected to have NASH with F2, F3 or F4 fibrosis in the United States by 2030, with over ten million aggregate individuals in France, Germany, Italy, Spain, the United Kingdom, and Japan. This rapid growth in advanced fibrosis reflects the impact of the late 20th century obesity epidemic, leading patients over time to progress through NAFLD to advanced NASH.

Emerging therapies in development

There are no therapies currently approved for the treatment of NASH. The current standard of care is diet and exercise. Although diet and exercise are effective for some patients in the treatment of NASH when maintained, adherence to this treatment regimen is generally poor. In addition, according to studies in Gastroenterology (2016) and the New England Journal of Medicine (2021), a substantial portion of patients who achieve significant weight loss do not experience fibrosis regression and, among those who do reverse fibrosis, it typically takes 4-5 years.

The multistep progression of NASH pathogenesis offers a variety of potential approaches for therapeutic intervention and many of these approaches have been explored with one or more therapeutic candidates. During the last few years, many NASH therapeutic candidates have had discouraging clinical trial results due to unfavorable efficacy and/or safety results; a substantial number of programs have been discontinued. Disappointing clinical results have especially been associated with therapeutic candidates designed to target late-stage disease by mitigating inflammation and reversing fibrosis, which have been labeled as “anti-fibrotic” mechanisms. Available data suggest that focusing only on suppressing inflammation and fibrosis is unlikely to deliver sustained reversal of fibrosis or resolution of NASH because the processes underlying NASH pathogenesis are not being addressed.

Clinical data has been more promising for “metabolic” therapeutic mechanisms that target earlier-stages of NASH pathogenesis, including excessive liver fat accumulation. Recent data for metabolic therapeutic candidates are consistent with data from anti-viral treatment of hepatitis C and modification of diet and exercise as a treatment for NASH. In each of these two cases, targeting the processes underlying inflammation and fibrosis of the liver can lead to reversal of fibrosis, even without a directly anti-fibrotic intervention. However, some of the encouraging data for metabolic therapeutic mechanisms has been offset by unwanted side effects, which may limit their ability to be used as treatment for patients with NASH. For instance, some NASH candidates have been shown to substantially increase plasma levels of low-density lipoprotein cholesterol, or LDL-C, or triglycerides, each of which is an independent causal risk factor for cardiovascular disease. Patients with NASH are already at increased risk for cardiovascular events. We therefore believe interventions that could be associated with increased cardiovascular risk may struggle to gain marketing approval from regulatory authorities and, if approved, may not be prescribed widely by treating physicians.

We believe the greatest potential for effective NASH treatment requires addressing both the late-stage fibrosis and the underlying processes of NASH pathogenesis with a favorable cardiovascular profile and without increasing the potential for drug-drug interactions associated with small molecules. Some NASH candidates are being evaluated for use in combination with one or more other investigational or marketed drugs to intervene at different stages of NASH pathogenesis and manage unwanted side effects. However, combining multiple interventions, particularly multiple small molecules, places an additional burden of drug metabolism and clearance upon already stressed hepatocytes.

We believe EFX has unique properties with the potential to address the complex pathogenesis of NASH as a foundational monotherapy: reducing liver fat, restoring metabolic balance, and reversing fibrosis while simultaneously improving independent risks of cardiovascular disease, without worsening any aspect of NASH pathogenesis.

Harnessing FGF21's Natural Metabolic and Anti-Fibrotic Effects

EFX harnesses the natural properties of FGF21 as a potential treatment for NASH. Specifically, EFX has been engineered to overcome the limitations of endogenous FGF21 by extending half-life from less than two hours to 2.5-3.5 days while maintaining FGF21's natural role in alleviating cellular stress and regulating whole-body metabolism. Consequently, EFX has the potential to address the underlying metabolic disease drivers of NASH while also reversing liver fibrosis. We believe EFX has the potential to be the leading FGF21 analog that most closely mimics the native protein with a long half-life that supports convenient weekly dosing.

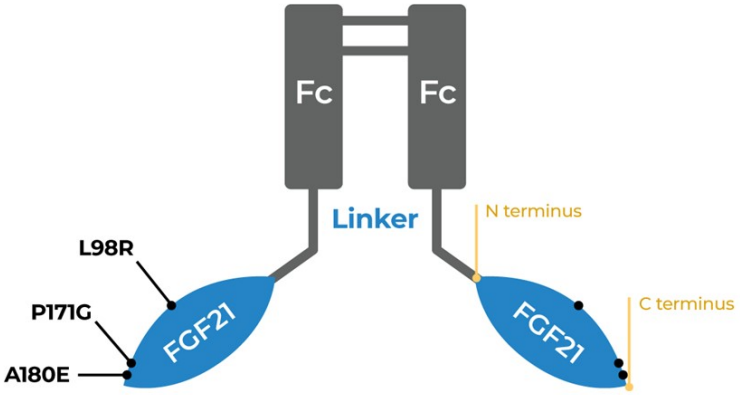
Overview of FGF21 biology

Fibroblast growth factors, or FGFs, are a large family of cell-signaling proteins involved in the regulation of many processes within the body. FGF21 is part of a sub-family of FGFs, known as endocrine FGFs, which are unique among FGFs because they initiate their biological effects by binding tightly to a cell surface receptor known as Beta Klotho, or Klotho. After this initial binding, FGF21 triggers signaling pathways within cells, such as hepatocytes and adipocytes, by binding to a second class of cell-surface receptor, known as the FGF receptors, or FGFRs. FGF21 binds to three specific FGFRs, known as FGFR1c, FGFR2c and FGFR3c. Once a co-receptor complex has formed with Klotho and one of the FGFRs, a series of intracellular signaling cascades is initiated. These signaling cascades enable FGF21 to exert its biological functions, which include regulation of energy homeostasis, glucose-lipid-protein metabolism and insulin sensitivity, and modulation of pathways that mitigate against intracellular stress. FGF21 cannot signal through cell membranes without both an intact C-terminus and an intact N-terminus to bind, respectively, to Klotho and FGFR. We believe EFX has been engineered to maximize binding at both the C-terminus and N-terminus, which distinguishes EFX from other FGF21 analogs.

EFX is designed to overcome the limitations of native FGF21 as a therapeutic

EFX has been engineered to overcome the limitations of native FGF21 while retaining balanced agonism across FGFR1c, FGFR2c and FGFR3c. Specifically, EFX delivers: (1) protection against proteolysis and reduction of renal clearance, (2) an increased half-life from less than two hours to 2.5 to 3.5 days, (3) minimization of the potential for aggregation in solution and (4) improved binding affinity for Klotho. These attributes are accomplished through a combination of three amino acid substitutions in the FGF21 protein sequence and an Fc-fusion protein scaffold similar to the platform used for Enbrel and Trulicity. As illustrated in the figure below, each EFX molecule consists of two Fc-FGF21 molecules linked by two disulfide bridges. The N-terminus of the FGF21 moiety is connected to the Fc portion of EFX through a polyglycine-serine linker. Our patents include claims directed to Fc fusion with a recombinantly modified FGF21 as well as claims directed to an FGF21 polypeptide comprising combinations of point mutations at positions 98, 171 and 180 of mature human FGF21. Pharmacokinetic modeling based on analysis of intact, active EFX in human serum after weekly administration of EFX for 16-24 weeks in the Phase 2a BALANCED and Phase 2b HARMONY studies indicates steady-state exposure is attained between weeks 4 and 8. More than a two-fold increase in exposure to EFX is observed for 50mg relative to 28mg despite a less-than-two-fold increase in dose.

Protein engineering of EFX



Based on recent in vitro analysis as well as the robust results of clinical trials evaluating EFX, we believe the bivalent structure of EFX, with two FGF21 monomers covalently linked via the disulfide bridges of the Fc fragment, may confer a longer duration of pharmacological activity relative to analogs of FGF21 based on single chain configurations. The in vitro tests analysis demonstrated that the bivalent configuration was associated with a 100-fold greater affinity of EFX for the signaling receptor complex than corresponding single chain configurations.

EFX maintains balanced agonism of FGFR1c, FGFR2c and FGFR3c to mimic native FGF21

EFX was designed through an empirical discovery process that incorporated in vitro and in vivo measurements of receptor agonism to assess which of many tested discovery candidates yielded the most attractive drug properties. EFX was selected for clinical evaluation over other discovery candidates, which included a proprietary PEGylated FGF21 analog and two versions of a two-point mutation Fc-fusion protein known as RG (with mutations at positions 98 and 171, but not 180), one of which had the Fc fused to the C-terminus while the other had it fused to the N-terminus of the modified FGF21. In comparative in vitro receptor agonism assays, EFX exhibited the greatest potency for each of FGFR1c, FGFR2c, and FGFR3c among the candidates tested. Furthermore, the potency of EFX for FGFR1c, FGFR2c and FGFR3c was comparable to that of recombinantly-expressed human FGF21.

In vitro receptor agonism assays do not necessarily predict receptor binding when administered in humans. We therefore believe human clinical data is necessary to confirm whether balanced agonism of the FGF receptors is truly achieved. Because certain FGF receptors are expressed predominantly in liver tissue while others are expressed predominantly in peripheral tissue, the extent of binding to different receptors can be assessed from the pharmacodynamic effects in human clinical trials. Increases in adiponectin, for example, depend on activation of FGFR1c in adipose tissue. We believe EFX's balanced effects when administered in human clinical trials confirm that EFX's unique engineering results in balanced agonism in vivo as well as in vitro.

The effects observed in clinical trials with EFX contrast with observations from clinical trials evaluating certain pegylated or glycopegylated FGF21 analogs, which we believe may be attributed to the potential for pegylated moieties to accumulate in the liver. For example, each of two FGF21 analogs for which histology results have been reported publicly, one of which is pegylated and one of which is glycopegylated, were observed to have substantially lower rates of fibrosis improvement than observed with EFX. We also observed more substantial reductions in triglycerides and increases in adiponectin than was reported for these two FGF21 analogs, among other measures. We believe the unique and proprietary engineering of EFX, including its targeted amino acid substitutions and Fc fusion scaffold, as described

above, may be responsible for the differentiated clinical effects observed after treatment with EFX compared with other pegylated FGF21 analogs.

EFX exerts both metabolic and anti-fibrotic effects with a favorable cardiovascular profile

We believe intervening across the core processes underlying NASH pathogenesis is the most effective way to restore health to the liver of patients with NASH and reduce the risk of cardiovascular disease, which is the leading contributor to mortality and morbidity among these patients. By mimicking FGF21, EFX has the potential to intervene in each of the core processes underlying NASH pathogenesis acting as both a metabolic and anti-fibrotic therapeutic agent. EFX acts to leverage whole-body metabolism to redirect calories away from the liver to peripheral tissues, including adipose tissue, thereby reducing fat deposited in the liver and decreasing the rate of fat oxidation by the liver. Through this activity, EFX reduces fibrosis both indirectly, as a result of alleviating hepatocyte stress, and directly, by suppressing local inflammation and activation of collagen secreting myofibroblasts that lay down fibrotic tissue.

Overview of EFX Clinical Development

We have two active EFX programs supported by two ongoing, parallel Phase 2b clinical trials: the HARMONY study in pre-cirrhotic patients with F2-F3 fibrosis and the SYMMETRY study in patients with cirrhosis due to NASH (F4, compensated). Each of our two Phase 2b clinical trials is precedented by Phase 2a data in patients with biopsy-confirmed NASH. We believe that the longer study durations of 24 and 36 weeks in our Phase 2b trials, compared with 16 weeks for the BALANCED study, are likely to show a further improvement in resolution of fibrosis and NASH.

Summary of Completed and Ongoing EFX Clinical Trials in Patients with NASH

EFX has been administered to a total of 244 adult patients with either NASH or T2D for up to 96 weeks in four randomized, double-blind, placebo-controlled clinical trials for which results have been reported. In addition, approximately 120 NASH patients are estimated to be treated with EFX in a fifth study that is currently blinded and remains ongoing. Three of these clinical trials have been completed: (a) a single-ascending dose study in patients with T2D, (b) a four-week, multiple-ascending dose study in patients with T2D, and (c) the Phase 2a BALANCED study in patients with NASH, which consisted of a main study in patients with pre-cirrhotic (F1-F3) NASH and an expansion cohort in patients with cirrhosis (F4, compensated). Two clinical trials are ongoing: (d) the Phase 2b HARMONY study in patients with pre-cirrhotic NASH (F2-F3), in which the primary efficacy endpoint was measured at week 24 and patients continue treatment with EFX or placebo for up to 96 weeks and (e) the Phase 2b SYMMETRY study in patients with cirrhosis due to NASH (F4, compensated), for which the primary endpoint will be measured at week 36 and patients will continue treatment with EFX or placebo for up to 96 weeks. We believe the combined results reported to date from these trials provide compelling evidence for EFX's potential to address all core aspects of NASH pathogenesis. If approved, we believe these attributes of EFX may allow it to emerge as a foundational NASH monotherapy.

EFX for Treatment of Pre-Cirrhotic NASH (F2-F3)

Our lead program focuses on development of EFX for treatment of pre-cirrhotic NASH (F2-F3 fibrosis). The ongoing Phase 2b HARMONY study in patients with F2-F3 fibrosis is precedented by data from the previously completed Phase 2a BALANCED study in patients with F1-F3 fibrosis.

Phase 2b clinical trial of EFX in patients with biopsy-confirmed F2-F3 NASH

The Phase 2b HARMONY study is a multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial in biopsy-confirmed adult NASH patients with fibrosis stage 2 or 3. The study enrolled a total of 128 patients, randomized to receive once-weekly subcutaneous dosing of 28mg or 50mg EFX, or placebo for 24-weeks. The primary efficacy endpoint for the study was the proportion of subjects who achieve at least a one-stage improvement in fibrosis without worsening of NASH at week 24. Key secondary histology endpoints consisted of NASH resolution without worsening of fibrosis and a composite endpoint of both NASH resolution and fibrosis improvement at week 24. Additional secondary measures included change from baseline in liver fat, markers of livery injury, noninvasive markers of liver fibrosis, glycemic control, lipoproteins, and body weight at 24 weeks as well as safety and tolerability measures.

HARMONY biopsy analysis and definition of histology endpoints

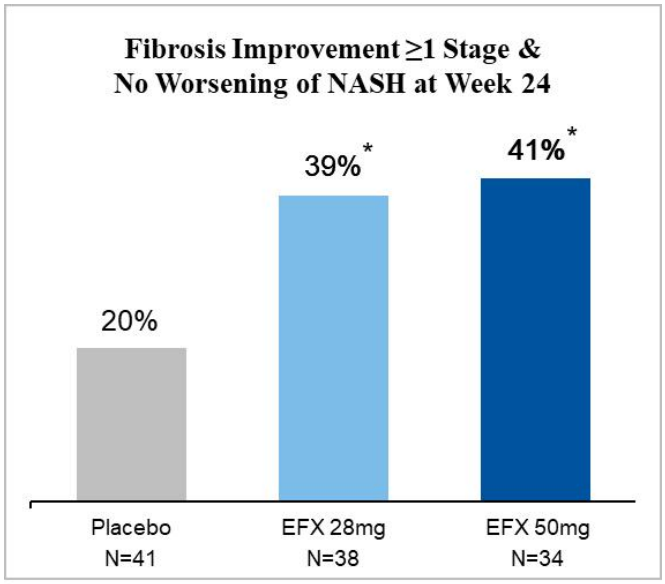
Consistent with FDA recommendations, the HARMONY study evaluated all biopsies using consensus readers. Two independent and cross-trained pathologists scored each biopsy for NAS score and fibrosis stage. If there were any differences on any component of pathology scoring, the two pathologists met to determine if consensus could be reached. In the absence of consensus, a third pathologist would adjudicate between the first two pathologists' scores. Adjudication by a third pathologist was not required because the two principal pathologists achieved consensus on interpretation of all HARMONY biopsy samples.

Per applicable FDA guidance regarding endpoints recommended for use in Phase 3 clinical trials evaluating pre-cirrhotic NASH, the HARMONY study's primary and key secondary histology endpoints were defined as:

- Proportion of subjects who achieve improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis)
- Proportion of subjects who achieve resolution of steatohepatitis (defined as a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis) and no worsening of liver fibrosis on NASH CRN fibrosis score.
- Proportion of subjects who achieve improvement in liver fibrosis greater than or equal to one stage and no worsening of steatohepatitis (as defined above).

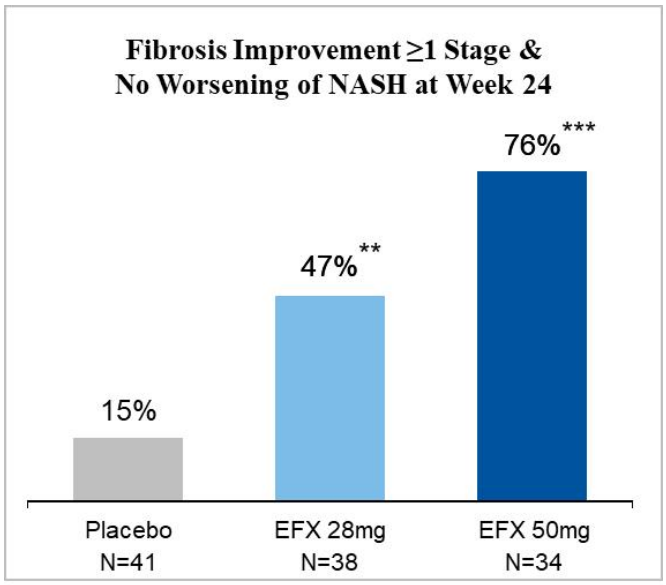
Both the 50mg and 28mg EFX doses achieved statistical significance on primary and secondary histology endpoints

The HARMONY study met its primary endpoint for both the 50mg and 28mg EFX dose groups, with 41% and 39% of EFX-treated patients, respectively, experiencing at least a one-stage improvement in liver fibrosis with no worsening of NASH by week 24, compared with 20% for the placebo arm.



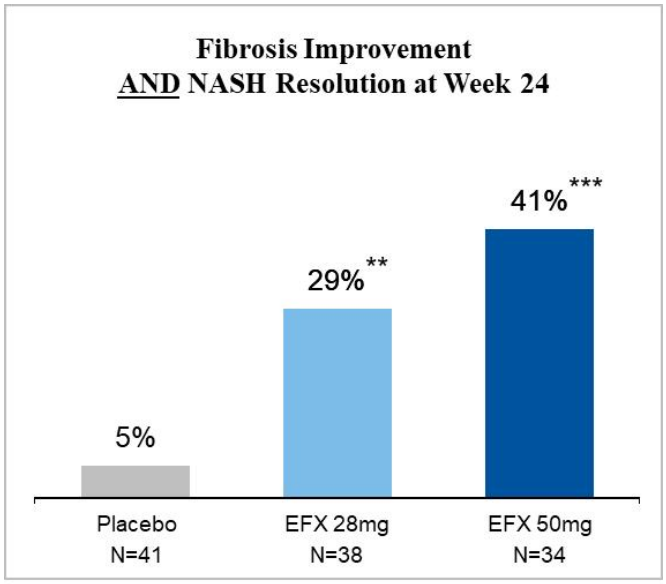
* p<0.05, versus placebo (Cochran–Mantel–Haenszel test [CMH])
Source Data: Liver Biopsy Analysis Set

The study also met a key secondary endpoint with 76% and 47% of patients treated with 50mg and 28mg, respectively, achieving NASH resolution without worsening of fibrosis, compared with 15% for placebo.



** p<0.01, *** p<0.001, versus placebo (CMH)
Source Data: Liver Biopsy Analysis Set

In addition, 41% and 29% of patients treated with 50mg and 28mg, respectively, achieved both endpoints (NASH resolution and fibrosis improvement ≥1 stage), compared with 5% for placebo.



** p<0.01, *** p<0.001, versus placebo (CMH)
Source Data: Liver Biopsy Analysis Set

EFX reduced liver fat

As summarized in the table below, highly statistically significant relative reductions of 52 to 64 percent of liver fat were observed for the 28 and 50mg dose groups, respectively, compared with a 6 percent reduction for placebo.

Roughly two-thirds of EFX patients achieved at least a 50 percent relative reduction in liver fat and one-third to one-half of EFX patients normalized their liver fat levels, which is defined as reaching less than or equal to 5 percent absolute liver fat content at week 24 with a baseline level of greater than 5 percent. Based on the results of additional post-hoc analyses of liver fat reduction, we believe normalization of liver fat, rather than a relative reduction of at least 30 percent liver fat may be a more reliable predictor of histological improvement, particularly NASH resolution.

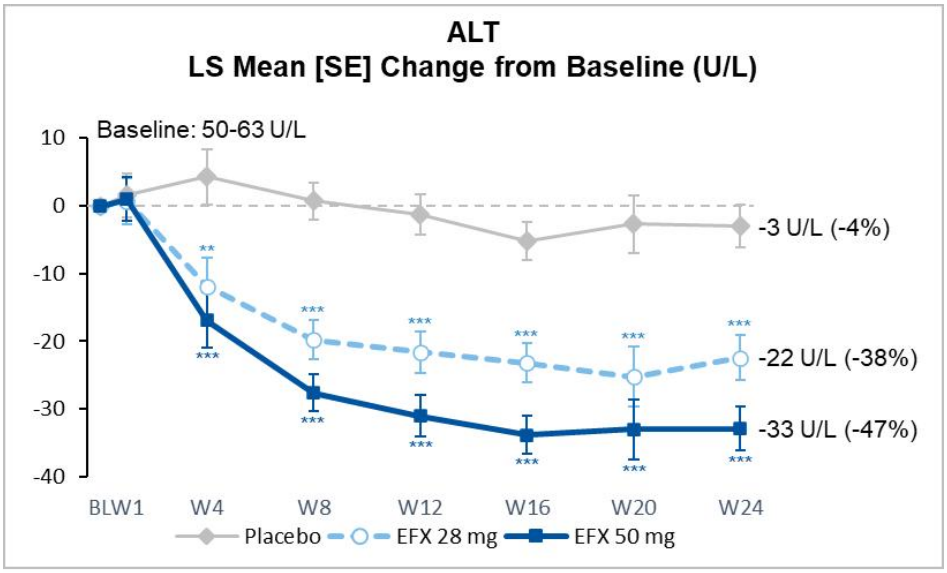
Summary of Week 24 Liver Fat Endpoints

		EFX (once weekly dose)	
Measure (LS Mean)	**Placebo** (N=42)	**28 mg** (N=38)	**50 mg** (N=35)
Relative change in liver fat[1] (%)	-6	-52***	-64***
Proportion of Patients	**Placebo** (N=42)	**28 mg** (N=38)	**50 mg** (N=35)
≥50% relative reduction in fat[2] (%)	2	63***	77***
≤ 5% absolute liver fat[2] (%)	2	34***	51***

***p<0.001, versus placebo (ANCOVA [relative change] or CMH [≥50% relative change and ≤5% absolute])
Source Data: MRI-PDFF Analysis Set (all patients who have Baseline and Week 24 liver fat measurements)

EFX improved markers of liver injury

The substantial reductions in liver fat among EFX patients correlated with various markers of liver health, including the liver enzyme ALT, as shown in the figure below. The 28 and 50mg EFX groups achieved highly statistically significant ALT reductions by week 8, with reductions of 38 percent and 47 percent, respectively, at week 24, compared with a 4 percent reduction for placebo. Similar dose-related improvements were observed for other liver health markers, including AST, GGT, ALP, and uric acid. We believe the rapid and sustained reductions in ALT are particularly noteworthy as reductions have been positively correlated with histological response.



** p<0.01, *** p<0.001, versus placebo (MMRM)
Source Data: Full Analysis Set

EFX improved noninvasive markers of liver fibrosis

EFX was observed to significantly improve two important noninvasive markers of liver fibrosis. Pro-C3 is a serum biomarker of collagen synthesis and fibrogenesis in the liver. The Enhanced Liver Fibrosis, or ELF, score is a

composite biomarker that has strong correlations with fibrosis stage. Reductions in Pro-C3 indicate lower levels of new fibrosis formation while reductions in the ELF score suggest lower overall fibrosis. Pro-C3 and the ELF score are clinically important because they 1) quantitate fibrotic activity throughout the liver rather than in a small biopsy of the liver and 2) are noninvasive and therefore can be measured repeatedly over time, thus overcoming two core limitations of biopsy-based histopathology. As shown in the table below, highly significant absolute reductions in Pro-C3 of about 5 ug/L were observed for both EFX dose groups, compared with a nominal increase for placebo. As shown in the same table below, we also observed highly significant reductions in ELF score of 0.6 to 0.7 were observed for the 28 and 50mg EFX dose groups, respectively, compared with a nominal increase for placebo.

Summary of Week 24 Noninvasive Measures of Liver Fibrosis

Dose Group	**Placebo (n=40-42)**	**28mg (n=37-38)**	**50mg (n=34-36)**
Pro-C3 (µg/L)	+0.1	-5.1***	-5.2***
ELF Score	+0.1	-0.6***	-0.7***
Liver Stiffness by FibroScan (kPa)	-0.7	-2.6†	-4.3**

***p<0.001, versus placebo; † p<0.01, versus baseline (ANCOVA[2])
Source Data: Full Analysis Set

EFX improved glycemic control, reduced body weight and restored a healthy lipoprotein profile

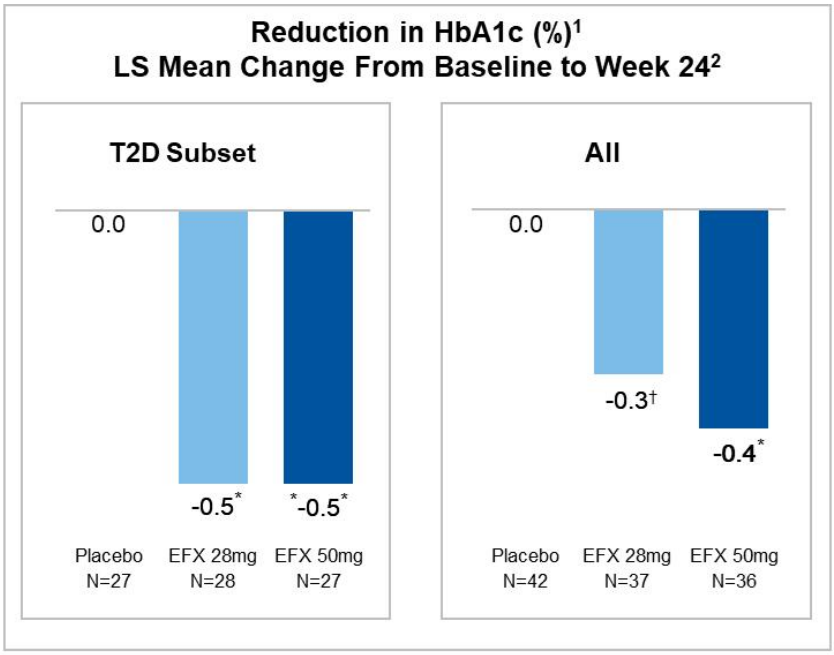
As summarized in the following table, treatment with EFX was also associated with significant improvements in multiple metabolic parameters, including markers of glycemic control, body weight, and lipoproteins. This favorable metabolic profile is important because cardiovascular disease remains the greatest mortality risk for patients with NASH. The HARMONY study shows that EFX has the potential to be consistent with the FDA guidance by improving multiple metabolic parameters.

Summary of Week 24 Cardio-Metabolic Biomarkers

Measure (LS Mean Change From Baseline to Week 24)[1]	**Placebo (N=42)**	**28 mg (N=37)**	**50 mg (N=36)**
HbA1C (%, absolute)	0.0	-0.3†	-0.4*
Body Weight (kg)	-0.6	-0.2	-2.9††
Triglycerides (%)	+9	-25***	-29***
HDL Cholesterol (%)	-2	+24***	+30***
Non-HDL Cholesterol (%)	+8	-13***	-13***
LDL Cholesterol (%)	+9	-8**	-8**

**p<0.01, ***p<0.001, versus placebo; ††p<0.01, versus baseline (ANCOVA[2])

EFX's potential to improve glycemic control is an important feature of its therapeutic profile because approximately two-thirds of patients with F2-F3 fibrosis have T2D, which is generally poorly controlled. FDA encourages later-stage NASH clinical trials to stratify for T2D status, signifying the importance of assessing the impact of any therapy on patients with both NASH and T2D. EFX treatment resulted in absolute reductions in HbA1c of 0.3% and 0.4% for the 28 and 50mg doses, respectively, compared with no change for placebo. These results exceeded our expectations because EFX was dosed on top of antidiabetic medications for the approximately two-thirds of patients in the study with T2D. EFX's insulin sensitizing benefits are seen more clearly in the subpopulation of patients with T2D, who had reductions in HbA1c of 0.5 for both EFX dose groups, compared with no change for placebo.



* p<0.05, versus placebo (MMRM); † p<0.05, versus baseline (MMRM)
[1] Absolute change from baseline, %; [2] Patients remained on diabetic medications
Source Data: Biomarker Analysis Set

The overall improvement in glycemic control is consistent with observations previously reported by Amgen after treating T2D patients for 4 weeks, as well as observations from our Phase 2a BALANCED study in patients with pre-cirrhotic NASH (F1-F3), underscoring the reproducibility of this effect. Achieving better glycemic control by improving insulin sensitization is highly desirable because it is rectifying a fundamental driver of T2D, which is insulin resistance. This means EFX has the potential to achieve a sustained reduction in HbA1c, in contrast to diabetes therapies that promote insulin secretion whose efficacy tends to wane over time.

The improvement in glycemic control at 50mg was accompanied by a mean reduction in body weight of 2.9kg after 24 weeks, corresponding to 2.6 percent decrease. The trend toward weight loss observed with EFX contrasts with another class of insulin sensitizers, the PPAR gamma agonists. This class includes established antidiabetic drugs like pioglitazone, whose use has declined substantially because of weight gain and edema, and lanifibranor, which has been associated with weight gain of about 2.4-2.7kg and 6 to 8% edema. The weight loss observed with EFX also contrasts with the weight gain observed with another FGF21 analog targeting only the FGFR1c receptor. We believe the potential for weight loss will be attractive to clinicians and NASH patients.

These encouraging metabolic data are best viewed holistically rather than in isolation. The HARMONY study, similar to the BALANCED study, showed that EFX has the potential to rectify each aspect of the metabolic dysfunction associated with NASH: improved glycemic control through enhanced insulin sensitivity, restoration of a healthy lipoprotein profile and reduced body weight. These broadly based improvements increase our confidence that the rapid reduction of steatohepatitis and collagen deposition seen in HARMONY and BALANCED could be sustained over longer treatment periods. The magnitude of metabolic improvements, particularly regarding lipoproteins that are associated with increased risk of cardiovascular disease, also points to the potential of EFX to achieve meaningful reductions in markers of cardiovascular risk.

In summary, while head-to-head preclinical studies and clinical trials have not been conducted, we believe the breadth of desirable clinical effects elicited by EFX sets it apart from other candidates in development for NASH, which frequently trade off efficacy improvements against detrimental effects on lipoproteins, increased body weight, and/or no improvement in glycemic control. With EFX, we see potential to restore a healthy metabolic profile not only to the liver,

but also to the whole body. The results are consistent with our predictions based on FGF21 biology and EFX's engineering.

EFX was generally well tolerated

EFX was generally well tolerated in the HARMONY study. There were no deaths in the study, one drug-related Serious Adverse Event, or SAE, and three non-drug-related SAEs. Across EFX groups, the most frequent Adverse Events, or AEs, were grade 1 or 2 gastrointestinal events, which were transient in nature. There were two discontinuations due to drug related AEs in each of the 28 and 50 mg EFX groups and no discontinuations due to the most common AE, diarrhea, in the 50mg EFX group. No clinically significant, dose-dependent changes compared to placebo were identified based on laboratory parameters or electrocardiograms. There were no notable or dose-dependent changes in respiratory rate or heart rate. Although transient increases in systolic blood pressure were noted during the study, no dose response was observed, and change from baseline at week 24 was not significantly different compared to baseline or placebo in either dose group.

As with all therapeutic proteins, there is potential for immunogenicity following treatment with EFX. The detection of anti-drug antibody, or ADA, formation is highly dependent on the sensitivity and specificity of the assay. Our current EFX ADA assay is more than 10 times more sensitive than the minimum FDA requirements. Pre-existing baseline antibodies to EFX were detected in 8.7% of patients. In the evaluable subjects receiving at least 1 dose of EFX, our assay detected the formation of ADAs in roughly 83% of EFX patients, compared with 5% in the placebo group. Importantly, measured antibody titers were largely low or very low, occasionally moderate, and developed slowly. No association was discernable between antibody titer and serum levels of EFX, nor was there a discernable association between tolerability and therapeutic response to EFX.

Phase 2a clinical trial of EFX in patients with biopsy-confirmed F1-F3 NASH

The main portion of the Phase 2a BALANCED study was a multicenter randomized, double-blind, placebo-controlled, dose-ranging clinical trial in adult patients with biopsy-confirmed NASH (F1-F3), a NAS score of at least 4, and baseline liver fat of at least 10% on MRI-PDFF screening. Patients were randomized to receive once-weekly subcutaneous doses of either 28, 50 or 70mg of EFX (n=59) or placebo (n=21) for 16 weeks. The primary endpoint was absolute reduction in liver fat at week 12 as measured by MRI-PDFF. Additional secondary and exploratory measures included noninvasive measures of liver function, fibrosis biomarkers, insulin sensitivity, lipoproteins and body weight, as well as histological measures based on liver biopsies.

As summarized in the table below, showing placebo-corrected results for the BALANCED and HARMONY studies, the results were largely comparable across the two studies.

		Placebo	EFX 28mg		EFX 50mg	
% Responders, Histology and Liver Fat Normalization		HARMONY	BALANCED	HARMONY	BALANCED	HARMONY
Fibrosis improvement ≥ 1 stage and no worsening of NASH		20	46	39	62	41
NASH resolution and no worsening of fibrosis		15	46	47	54	76
Fibrosis improvement AND resolution of NASH		5	31	29	39	41
Normalization of liver fat to ≤5%		5	21	34	45	51
Non-Invasive Tests			BALANCED[a]	HARMONY[b]	BALANCED[a]	HARMONY[b]
Placebo-Adjusted LS Mean Absolute Change	Pro-C3 (µg/L)		-5.3	-5.2	-3.9	-5.3
	ELF Score		-0.7	-0.7	-0.8	-0.8
	Liver Stiffness (kPa)		n/a[#]	-1.9	-3.8[#]	-3.6
	Body Weight (kg)		-0.2	0.4	-2.2	-2.3
	HbA1c, % (T2D subset)		0.1	-0.5	-0.6	-0.6
Placebo-Adjusted LS Mean Relative Change (%)	C-peptide		-44.9	-25.2	-42.9	-31.7
	Adiponectin		72.8	33.9	92.2	80.8
	Liver Fat Content		-63.0	-45.5	-70.6	-57.6
	ALT		-41.2	-34.1	-50.8	-43.6
	AST		-40.1	-37.6	-45.5	-47.4
	Triglycerides		-43.0	-34.0	-51.4	-37.2
	LDL Cholesterol		-15.6	-16.9	-2.1	-16.2
	Non-HDL Cholesterol		-20.6	-20.2	-13.1	-20.7
	HDL Cholesterol		29.8	25.8	34.6	32.1

[a] Change from baseline to week 12 (ELF, Liver Fat) or week 16 (all other endpoints); [b] Change from baseline to Week 24; [#] Change in Liver Stiffness in BALANCED was only assessed in Cohort C in patients with cirrhotic NASH

EFX was generally well tolerated in the BALANCED study. There were no deaths in the study and two SAEs, one of which occurred prior to dosing and the second of which was related to acute pancreatitis in a patient who was morbidly obese with high insulin resistance at baseline. Across EFX groups, the most frequent AEs were grade 1 or 2 gastrointestinal events, which were transient in nature. There were no discontinuations due to treatment-emergent AEs in the 50 mg dose group and none due to the most common AE, diarrhea.

EFX for Treatment of Cirrhosis Due to NASH

Cirrhosis due to NASH (F4, compensated) presents high unmet medical need, with approximately 50 percent of patients with cirrhosis dying within 5 years absent a liver transplant. This means the risk of liver failure and hepatocellular carcinoma, as well as need for liver transplantation, is substantially higher for cirrhotic patients. The FDA has issued draft guidance specific to the development of investigational therapies for patients with cirrhotic NASH, who are projected to number more than 3.5 million patients in the United States by 2030. According to the FDA, the treatment goal for cirrhotic patients is to halt disease progression, thereby preventing clinical decompensation, reducing the incidence of liver transplantation, and improving survival.

A recent analysis showed reversal of cirrhosis was associated with an 80% reduction in risk of liver-related clinical events, emphasizing the medical benefit to be gained if a therapy can reverse patients out of cirrhosis. To date, public reports of other investigational NASH drugs in clinical development for treatment of cirrhotic NASH have failed to demonstrate evidence of reversing fibrosis. However, we believe EFX has the potential to be the first therapy approved to treat patients with cirrhosis due to NASH, and to potentially reverse compensated cirrhosis.

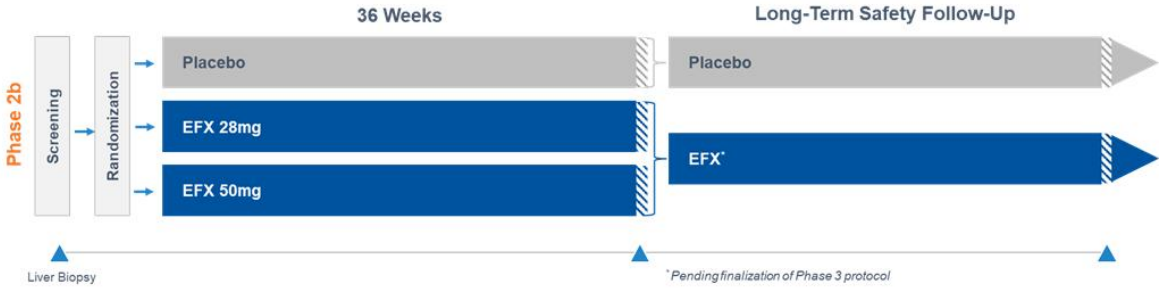
Our belief in EFX's potential to be an effective treatment for patients with cirrhosis due to NASH is based on the combined results of the BALANCED and HARMONY studies in patients with pre-cirrhotic NASH as well as the results of an expansion cohort of the BALANCED study evaluating patients with cirrhosis due to NASH.

Phase 2b clinical trial of EFX in patients with biopsy-confirmed cirrhotic NASH (F4, compensated) for 36 weeks

The Phase 2b SYMMETRY main study is a multicenter, randomized, double-blind, placebo-controlled, clinical trial in biopsy-confirmed NASH patients with compensated cirrhosis (F4, Child-Pugh class A). One hundred eighty-two patients have been randomized to receive once-weekly subcutaneous dosing of 28 or 50mg EFX, or placebo. The primary endpoint for the trial is fibrosis regression after 36 weeks treatment. Secondary measures include change from baseline in liver enzymes, liver fat, lipoproteins, glycemic control, and body weight at 36 weeks, as well as evaluation of

safety and tolerability. To provide additional safety data from long-term follow up, patients will continue to receive EFX or placebo from 36 to 96 weeks.

Phase 2b SYMMETRY study design



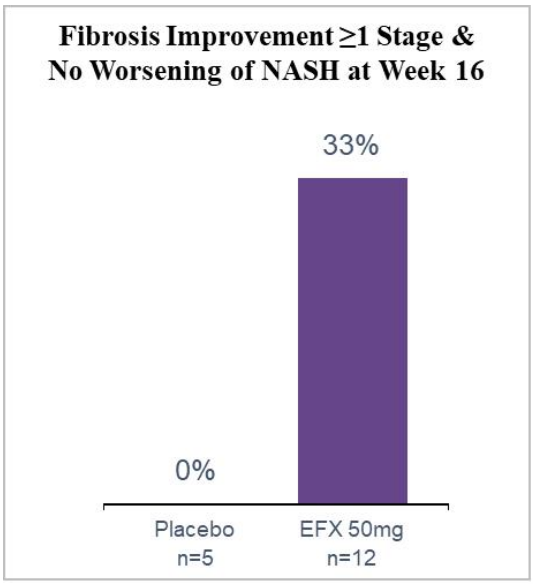
Phase 2a expansion cohort of EFX in patients with biopsy-confirmed cirrhotic NASH (F4, compensated)

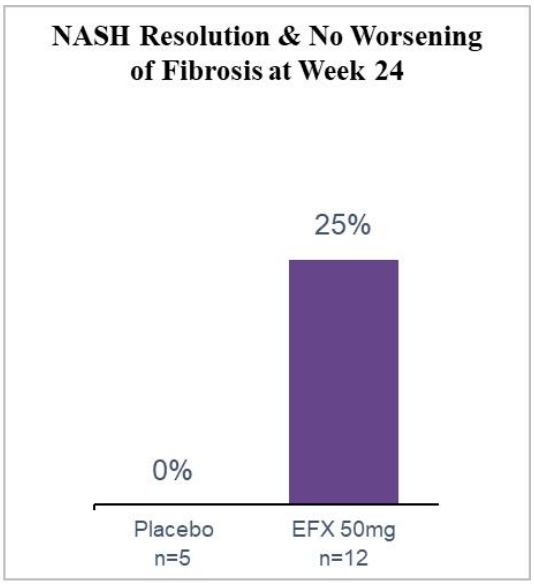
THE SYMMETRY study builds upon encouraging results from an expansion cohort of the BALANCED study evaluating EFX in patients with compensated cirrhosis (F4, Child-Pugh Class A), which was called Cohort C. Thirty patients were randomized in Cohort C to receive either EFX (n=20) or placebo (n=10) for 16 weeks. The primary endpoint was to assess safety and tolerability of EFX in treatment of patients with cirrhotic NASH. Additional noninvasive efficacy measures were included as secondary and exploratory endpoints, including liver enzymes, markers of liver fibrosis, and measures of insulin insensitivity. The Cohort C protocol was amended to include voluntary end-of-treatment liver biopsies to assess whether histological improvements were evident after just 16 weeks of treatment.

EFX improved histology, as measured by fibrosis improvement and NASH resolution

Results were obtained from a total of 17 of the 30 Cohort C study participants who volunteered for end-of-treatment biopsies, including placebo (n=5) and EFX patients (n=12). The figure below shows the biopsy results for patients who achieved fibrosis improvement without worsening of NASH (33% of EFX patients compared with 0% of placebo patients), and NASH resolution without worsening of fibrosis (25% of EFX patients compared with 0% of placebo patients). There was no overlap between responders for each of these two endpoints. Accordingly, a total of 7 of 12 EFX patients, or 58%, showed histological improvements, compared with 0 of 5 placebo patients. We believe these results are encouraging given that they were obtained after only 16 weeks of treatment.

Cohort C Histological Improvements[1]





[1] Study not powered to assess statistical significance of histological endpoints
Source Data: Liver Biopsy Analysis Set (all patients with post-treatment liver biopsy results)

EFX improved noninvasive markers of liver fibrosis

As with the BALANCED main study, EFX was observed to significantly improve three important noninvasive markers of liver fibrosis among patients with cirrhosis due to NASH. These three measures complement the liver biopsy results because they quantitate fibrotic activity across the whole liver and were collected for all patients, not only those who volunteered for end-of-treatment biopsies. The improvements in noninvasive measures of liver fibrosis for all EFX-treated patients, as shown in the table below, appear consistent with the histological improvements observed for the subset of patients who volunteered for end-of-treatment biopsies.

Summary of Cohort C Noninvasive Measures of Liver Fibrosis
LS Mean Change From Baseline to Week 16

Endpoint	Placebo (n=10)	50mg EFX (n=20)
Pro-C3 (µg/L)	-3.4	-9.0*
ELF Score	+0.3	-0.4**
Liver Stiffness by FibroScan (kPa)	-1.9	-5.7††

*p<0.05, versus **p<0.01, versus placebo (ANCOVA); ††p<0.01, versus baseline (ANCOVA)
Source Data: Full Analysis Set (all Cohort C patients with baseline and interpretable on-study measures)

EFX improved glycemic control, reduced body weight and restored a healthy lipoprotein profile in patients with cirrhosis

As shown in the table below, EFX was observed to improve glycemic control, reduce body weight, and restore a healthy lipoprotein profile in patients with cirrhosis, with results comparable to those achieved in patients with pre-cirrhotic NASH (F2-F3) treated with EFX 50mg in the HARMONY study.

Summary of Cohort C and Main Study Cardio-Metabolic Biomarkers

	Cohort C (F4)		HARMONY (F2-F3)	
Measure (LS Mean Change From Baseline to Week 16[1])	**Placebo (N=10)**	**50 mg (N=20)**	**Placebo (N=42)**	**50 mg (N=35-36)**
HbA1C (%, absolute)	+0.1	-0.4*	0.0	-0.4*
Body Weight (kg)	+1.2	-2.2	-0.6	-2.9††
Triglycerides (%)	+1	-29**	+9	-29***
HDL Cholesterol (%)	+4	+33***	-2	+30***
Non-HDL Cholesterol (%)	+12	-14***	+8	-13**
LDL Cholesterol (%)	+16	-8	+9	-8**

*p<0.05, **p<0.01, ***p<0.001, versus placebo (MMRM); †† p<0.01, versus baseline (MMRM)
Source Data: Full Analysis Set

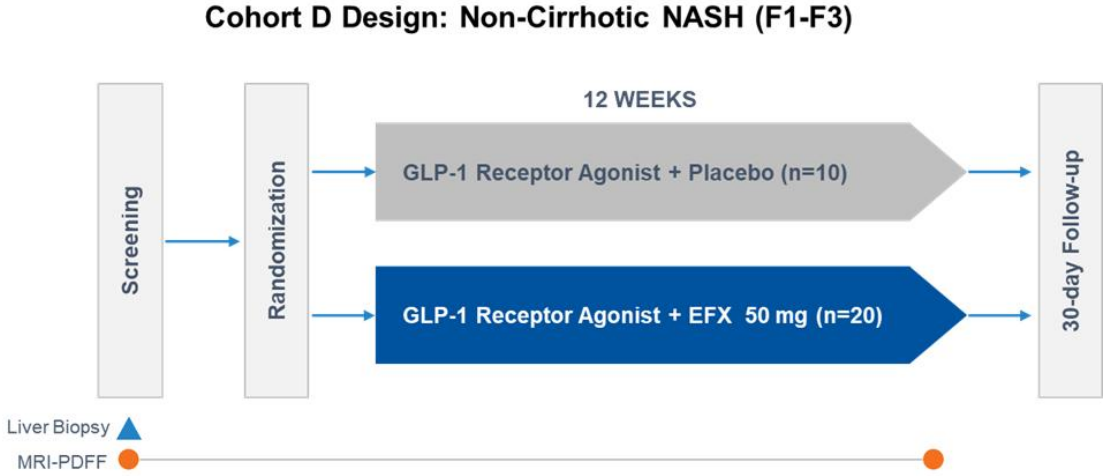
EFX was generally well tolerated

EFX was generally well tolerated in Cohort C. There were no deaths. One patient in the placebo arm reported an SAE of pulmonary embolism. One placebo patient withdrew consent and one patient in the EFX arm discontinued due to abdominal distension, constipation, diarrhea and pruritus. The most frequently reported study drug-related treatment-emergent AEs were transient mild-to-moderate diarrhea and nausea, which often resolved on study without treatment. All injection site reactions were grade 1.

Evaluation of EFX in combination with GLP-1 therapy in patients with pre-cirrhotic NASH

The SYMMETRY study includes an expansion cohort, known as Cohort D, evaluating administration of EFX to patients with T2D who are already being treated with GLP-1 therapy. The primary goal of the 12-week Cohort D expansion, in which 32 patients with T2D and F1-F3 liver fibrosis due to NASH have been randomized, is to assess safety and tolerability of EFX compared to placebo when added to an existing GLP-1 receptor agonist.

Future studies will evaluate the potential of EFX to accelerate resolution of NASH and reversal of fibrosis among NASH patients already on GLP-1 therapy, which could help address an urgent medical need to restore a healthy liver.



Exclusive license agreement with Amgen Inc.

In June 2018, we entered into an exclusive license agreement with Amgen Inc., or Amgen, pursuant to which we have been granted an exclusive, royalty-bearing license to certain intellectual property rights owned or controlled by

Amgen, to commercially develop, manufacture, use, distribute and sell therapeutic products, or Products. In particular, we have been granted licenses under patents filed in both the United States and foreign jurisdictions that are owned or controlled by Amgen, including an exclusive license under certain patents claiming polypeptides comprised of an FGF21 portion with certain point mutations, a linker, and an Fc domain. Our exclusively licensed patents include, but are not limited to, the composition of EFX and methods of using the same. In connection with the license, Amgen also licensed and transferred to us certain know-how related to the manufacture of EFX as well as certain quantities of EFX drug substance manufactured to Good Manufacturing Practices, or GMP, for clinical use, master cell bank, not-for-human use EFX drug product suitable for nonclinical studies and critical reagents.

Pursuant to the terms of the license agreement, we must use commercially reasonable efforts to develop and commercialize a Product in each of several major market territories. In addition, Amgen provided us, at its expense, consulting support in connection with the transfer of the licensed materials and the exploitation of the Products. We are also entitled to sublicense the rights granted to us under the license agreement.

As initial consideration for the license, we paid Amgen an upfront payment of $5.0 million and also issued 2,653,333 shares of our Series A preferred stock to Amgen at the time of the initial closing in June 2018 with a subsequent 3,205,128 shares of our Series A preferred stock issued at the time of the second closing in November 2018, representing 10% of total shares outstanding at such times. In August 2019 we made an additional payment of $2.5 million in connection with dosing the first patient in our Phase 2a clinical trial, which was the first development milestone under the license agreement. As additional consideration for the license, we are required to pay Amgen $7.5 million in connection with dosing the first patient in a Phase 3 clinical trial, up to $30.0 million in connection with marketing approvals, and aggregate milestone payments of up to $75.0 million upon the achievement of specified commercial milestones for all products licensed under the Amgen Agreement. No commercial milestones have been achieved to date under the license agreement. We are also required to pay tiered royalties of low to high single-digit percentages on annual net sales of the products covered by the license. The royalty rate with respect to the net sales is subject to customary reductions, including in the event that the exploitation of a Product is not covered by a valid claim with the licensed patent rights. The royalty term will terminate on a country-by-country basis on the later of (i) the expiration date of the last valid claim within the licensed patent rights, (ii) the loss of regulatory exclusivity in such country, and (iii) the tenth anniversary of the first commercial sale of such product in such country.

The license agreement shall expire upon the expiration of the last-to-expire royalty term for the Products in the territory. Upon expiration of the license agreement, the licenses granted to us shall be considered fully paid-up, irrevocable and non-exclusive. Either we or Amgen may terminate the license agreement if the other party commits a material breach of the agreement or defaults in the performance thereunder and fails to cure that breach within 90 days (or 30 days in the case of failure to make any payment as and when due under the agreement) after written notice is provided or in the event of bankruptcy, insolvency, dissolution or winding up. Amgen shall have the right to terminate the license agreement in full upon written notice to us in the event we, our affiliates or sublicensees, directly challenge the patentability, enforceability or validity of any licensed patents, unless, in the event of a sublicensee challenge, we terminate the sublicense within 60 days' notice. We shall have the right to terminate the license agreement within 90 days written notice to Amgen if we conclude, due to scientific, technical, regulatory or commercial reasons, that the exploitation of the Products is no longer commercially practicable.

Intellectual property

Our success depends in part upon our ability to protect our core technology and intellectual property. To protect our intellectual property rights, we rely on patents, trademarks, copyrights and trade secret laws, confidentiality procedures, and employee disclosure and invention assignment agreements. Our intellectual property is critical to our business and we strive to protect it through a variety of approaches, including by obtaining and maintaining patent protection in the United States and internationally for our product candidates, novel biological discoveries, new targets and applications, and other inventions that are important to our business. For our product candidates, we generally intend to pursue patent protection covering compositions of matter, methods of making and methods of use, including combination therapies. As we continue the development of our product candidates, we intend to identify additional means of obtaining patent protection that would potentially enhance commercial success, including through claims covering additional methods of use and biomarkers and complementary diagnostic and/or companion diagnostic related claims. As of March 6, 2023, we have licensed from Amgen Inc. approximately 184 patents and pending patent

applications worldwide, including 169 issued patents and 15 pending patent applications. There are currently no pending U.S. provisional patent applications.

As of March 6, 2023, our patent portfolio relating to EFX includes twelve issued U.S. patents, one pending U.S. patent application, and issued and pending foreign counterpart patents in Europe, Asia, Canada, Australia, and Mexico. Seven issued U.S. patents include claims directed to the EFX product, the FGF21 polypeptide component of the EFX product, nucleic acids encoding the product and related polypeptides, polypeptide multimers, related compositions, and methods of using EFX to, e.g., treat diabetes, lower blood glucose in patients suffering from a metabolic disorder, improve glucose tolerance, lower body weight, or reduce triglyceride levels in patients. These issued U.S. patents are expected to expire in 2029. The pending U.S. patent application and related foreign counterparts are directed to a method of treating a patient with non-alcoholic steatohepatitis (NASH); if issued, the resulting U.S. patent is expected to expire in 2029. We currently anticipate that a composition of matter patent will be eligible for patent term extension to 2034 in the U.S. The portfolio further includes five issued U.S. patents that are directed to related polypeptides and methods of use. An international patent application is pending relating to EFX formulations.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. However, trade secrets and know-how can be difficult to protect. We seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. The confidentiality agreements we enter into are designed to protect our proprietary information and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that we have executed such agreements with all applicable counterparties, such agreements will not be breached, or that these agreements will afford us adequate protection of our intellectual property and proprietary rights. For more information, see "Risk factors—Risks related to our intellectual property."

Manufacturing and supply

We manage several external commercial manufacturing organizations, or CMOs, to develop and manufacture EFX.

EFX drug substance, or DS, is manufactured by fermentation of a recombinant strain of the bacterium E. coli. Product accumulates as insoluble particles (inclusion bodies) within the cells and is recovered by cell disruption, followed by solubilization of the inclusion bodies, protein refolding and several chromatographic separation steps to yield product with target quality attributes. We have an agreement with Boehringer Ingelheim Biopharmaceuticals GmbH, or Boehringer Ingelheim, to manufacture DS for clinical development and plan to enter into a future agreement for commercial supply at an appropriate time. Whereas our Phase 2a BALANCED study was supplied by DS acquired by Amgen, our ongoing Phase 2b HARMONY and SYMMETRY studies are being supplied by DS manufactured by Boehringer Ingelheim. Analysis of the Boehringer Ingelheim GMP DS confirmed it met the same release specification as previously used for Amgen GMP DS and was comparable to Amgen GMP DS across a number of protein characterization studies.

We have an agreement with Vetter Pharma International GmbH, or Vetter, to manufacture EFX drug product, or DP, for clinical development and plan to enter into a future agreement for commercial supply at an appropriate time. The GMP DP being used for our ongoing HARMONY and SYMMETRY studies is similar to that for the BALANCED study, which was stored as a frozen liquid until immediately before administration to trial subjects. Analysis of the Vetter GMP DP confirmed that it met the same release specification as previously used for the DP manufactured from Amgen GMP DS.

We plan to use a newly developed lyophilized DP formulation for Phase 3 clinical trials and as the initial commercial presentation, if EFX is approved. This drug-device combination product, employing Vetter’s Lyo-Ject 3S dual-chamber syringe, was selected for convenient subcutaneous patient self-administration. Manufacturing of the product-device combination has been scaled up at Vetter and GMP lots have been released for use in Phase 3 clinical trials.

Sales and marketing

Successful marketing of a new drug for the treatment of NASH will require a targeted commercial infrastructure. We expect to begin making plans for commercialization in parallel with our ongoing HARMONY and SYMMETRY studies. We have also contracted with a third-party manufacturer, Vetter, to support clinical development and the potential commercialization of EFX with commercial-scale manufacturing. We intend to develop the commercial infrastructure required for bringing EFX to patients in the United States, if approved, in parallel with an anticipated Phase 3 clinical trial. We also plan to evaluate options for delivering EFX, if approved, to patients in other key markets, such as Europe, Japan and China, which may include strategic collaborations.

Competition

The biotechnology industry is intensely competitive and subject to rapid and significant technological change. Our competitors include multinational pharmaceutical companies, specialized biotechnology companies and universities and other research institutions.

We understand that a number of pharmaceutical companies, including AstraZeneca PLC/MedImmune LLC, Boehringer Ingelheim AG, Bristol-Myers Squibb Company, Inc., Eisai, Inc., Eli Lilly and Company, GSK plc, Johnson & Johnson, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Pfizer Inc., Roche Holding AG, Sanofi and Takeda Pharmaceutical Company Limited, as well as large and small biotechnology companies such as Albireo Pharma, Inc., Alnylam Pharmaceuticals, Inc., Altimmune, Inc., Amgen, Inc., Arrowhead Pharmaceuticals, Inc., Axcella Health, Inc., Boston Pharmaceuticals, Inc., Cirius Therapeutics, Inc., CohBar, Inc., CymaBay Therapeutics, Inc., 89bio, D&D Pharmatech, Inc., Enanta Pharmaceuticals, Inc., Galectin Therapeutics Inc., Galmed Pharmaceuticals Ltd., Gilead Sciences, Inc., Hanmi Pharmaceutical Company, Ltd., Intercept Pharmaceuticals, Inc., Inventiva Pharma SA, Ionis Pharmaceuticals, Inc., Madrigal Pharmaceuticals, Inc., MediciNova, Inc., North Sea Pharmaceuticals, Poxel SA, Sagimet Biosciences, Inc., Terns Pharmaceuticals, Inc. and Viking Therapeutics, Inc. are or may be pursuing the development or marketing of pharmaceuticals that target NASH. It is also probable that the number of companies seeking to develop products and therapies for the treatment of serious metabolic diseases, such as NASH, will increase. Many of our competitors have substantially greater financial, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior products. In addition, many of these competitors have significantly greater experience than we have in undertaking nonclinical studies and human clinical trials of new pharmaceutical products and in obtaining regulatory approvals of human therapeutic products. Accordingly, our competitors may succeed in obtaining FDA approval for superior products. Many of our competitors have established distribution channels for the commercialization of their products, whereas we have no such channel or capabilities. In addition, many competitors have greater name recognition and more extensive collaborative relationships. Smaller and earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies.

Our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidate or any future product candidates. Our competitors may also develop drugs that are more effective, more convenient, more widely used and less costly or have a better safety profile than our products and these competitors may also be more successful than we are in manufacturing and marketing their products. If we are unable to compete effectively against these companies, then we may not be able to commercialize our product candidate or any future product candidates or achieve a competitive position in the market. This would adversely affect our ability to generate revenue. Our competitors also compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Government Regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring, and post-approval reporting of biologics, medical devices and combinations of biologics and devices, or combination products, such as those we are developing. We, along with third-party contractors,

will be required to navigate the various nonclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates.

U.S. biological product development

In the United States, biological products are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies performed in accordance with the FDA's Good Laboratory Practice (GLP) regulation;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval of a clinical trial protocol and related documentation by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site before the trial may be initiated;
- performance of adequate and well-controlled human clinical trials according to FDA's regulations commonly referred to as Good Clinical Practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety, purity and potency of the proposed biologic product candidate for its intended use;
- preparation of and submission to the FDA of a Biologics License Application, or BLA, for MA that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with current Good Manufacturing Practices, or cGMPs, and to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity;
- potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA to permit commercial marketing of the product for particular indications for use in the United States.

Nonclinical and clinical development

Before testing any biological product candidate in humans, the product candidate enters the nonclinical testing stage. Nonclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product biological characteristics, chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the nonclinical tests must comply with federal regulations and requirements including GLP regulations and requirements.

Prior to beginning the first clinical trial with a product candidate, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. The IND also includes results of the nonclinical tests, including animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls (CMC) information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within the 30-day time period. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical trials due to, among other considerations, unreasonable or significant safety concerns, inability to assess safety concerns, lack of qualified investigators, a misleading or materially incomplete

investigator brochure, study design deficiencies, interference with the conduct or completion of a study designed to be adequate and well-controlled for the same or another investigational drug, insufficient quantities of investigational product, lack of effectiveness, or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing a clinical trial to begin, or that, once begun, issues or circumstances will not arise that delay, suspend or terminate such studies.

Clinical trials involve the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used in monitoring subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its related documentation before the clinical trial begins at that site, and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

A sponsor who wishes to conduct a clinical trial outside of the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of a BLA. The FDA may accept a well-designed and well-conducted foreign clinical study not conducted under an IND if the study was conducted in accordance with GCP requirements, and the FDA is able to validate the data through an onsite inspection if deemed necessary.

Clinical trials typically are conducted in three sequential phases that may overlap or be combined:

Phase 1—The investigational product is initially introduced into healthy human subjects. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. In the cases of some products for severe of life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in the targeted patient population.

Phase 2—The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning Phase 3 clinical trials.

Phase 3—The investigational product is administered to an expanded patient population to further evaluate dosage, to provide significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval or licensure and product labeling.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so called Phase 4 studies may be made a condition to approval of the BLA.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA and the

investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualified for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

BLA submission and review

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. FDA approval of a BLA must be obtained before a biologic may be marketed in the United States. The BLA must include all relevant data available from pertinent nonclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. The submission of a BLA requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the FDA accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Under the performance goals and policies implemented by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA targets ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. In both standard and priority reviews, the FDA does not always meet its PDUFA goal dates, and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews a BLA to determine, among other things, whether a proposed product is safe, pure and potent for its intended use, and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. Further, the FDA may convene an advisory committee to provide clinical insight on application review questions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve a product unless it determines that the manufacturing processes and facilities

are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP requirements. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for Fast Track designation, new biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address an unmet medical need for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new biologic may request the FDA to designate the biologic as a Fast Track product at any time during the clinical development of the product. One benefit of Fast Track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the FDA's breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, the FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

A product is eligible for priority review if it treats a serious or life-threatening disease or condition and has the potential, if approved, to provide a significant improvement in safety and effectiveness. The FDA will attempt to direct additional resources to the evaluation of an application for a new biological product designated for priority review in an

effort to facilitate the review. Under priority review, the FDA's goal is to review an application in six months once it is filed, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval (also referred to as Subpart E approval). Biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments, as demonstrated by a surrogate or intermediate clinical endpoint, may receive accelerated approval. Specifically, this means that they may be approved on the basis of clinical data establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA generally requires that a sponsor of a biological product receiving accelerated approval perform adequate and well-controlled post-marketing confirmatory clinical trials to verify the clinical benefit. Under the Food and Drug Omnibus Reform Act of 2022 ("FDORA"), the FDA is now permitted to require, as appropriate, that such trials be underway prior to approval or within a specific time period after the date of approval for a product granted accelerated approval, and the FDA has increased authority for expedited procedures to withdraw accelerated approval if, for example, the confirmatory trial fails to verify the predicted clinical benefit of the product. In addition, the FDA generally requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Pediatric information

Under the Pediatric Research Equity Act, a BLA or supplement to a BLA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers. A sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must submit an initial Pediatric Study Plan, or PSP, within 60 days of an end-of-Phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of the Phase 3 of Phase 2/3 study. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints, and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach an agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

Post-Approval requirements

Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements, under which the FDA assesses an annual program fee for each product identified in an approved BLA. Biologics manufacturers and their subcontractors, including those supplying products, ingredients, and components of them, 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 ongoing compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. For certain commercial prescription biologic products, manufacturers and other parties involved in the supply chain must also meet chain of distribution requirements and build electronic, interoperable systems for product tracking and tracing and for notifying the FDA of counterfeit, diverted, stolen and intentionally adulterated products or other products that are otherwise unfit for distribution in the United States. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

The FDA may withdraw 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 studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA closely regulates the marketing, labeling, advertising and promotion of biologics. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, regulate manufacturers' communications regarding off-label use of their products.

U.S. patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission data of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The United States Patent and Trademark Office, or U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Affordable Care Act, signed into law in 2010, 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. To date, a number of biosimilars have been licensed under the BPCIA, and numerous biosimilars have been approved in Europe. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered multiple times to an individual, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. Complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation of the abbreviated approval pathway that are still being worked out by the FDA.

Under the BPCIA, a reference biological product is granted a 12 year exclusivity period from the time of first licensure of the product. The FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and the FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the "first licensure" of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and impact of the BPCIA is subject to significant uncertainty.

Regulation of Combination Products in the United States

Certain products may be comprised of components, such as drug components, biologic components and device components, that would normally be regulated under different types of regulatory authorities, and frequently by different centers at the FDA. These products are known as combination products. Under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- a drug, or device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, or device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- any investigational drug, or device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Under the FD&C Act and its implementing regulations, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. The designation of a lead center generally eliminates the need to receive approvals from more than one FDA center for combination products, although it does not

preclude consultations by the lead center with another FDA center. The determination of which center will be the lead center is based on the "primary mode of action" of the combination product. The FDA has also established an Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute.

A combination product with biologic primary mode of action, such as a biologic dispensed in a pre-filled syringe, generally would be reviewed and licensed pursuant to the biologic licensing processes under the PHS Act. In reviewing the BLA application for such a product, however, FDA reviewers in the drug or biologics center could consult with their counterparts in the device center to ensure that the device component of the combination product meets applicable requirements regarding safety, effectiveness, durability and performance.

Following approval of a combination product, each component of a combination product retains its regulatory status (as a biologic or device, for example) and is subject to the requirements established by the FDA for that type of component. Accordingly, under FDA regulations, biologic-device combination products are subject to cGMP requirements applicable to both biologics and devices, including the cGMP requirements for biologics and the FDA's Quality System Regulation applicable to medical devices.

Other U.S. healthcare and Data Privacy laws and compliance requirements

In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended, as applicable.

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business that may constrain the financial arrangements and relationships through which we research, as well as sell, market and distribute any products for which we obtain MA. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, and transparency laws and regulations related to drug pricing and payments and other transfers of value made to physicians and other healthcare providers. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations, integrity oversight and reporting obligations, exclusion from participation in federal and state healthcare programs and responsible individuals may be subject to imprisonment.

Also, many states have similar, and typically more prohibitive, fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, as well as the California Consumer Privacy Act of 2018 (the "CCPA"), impose requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates, independent contractors, or agents of covered entities, which include certain healthcare providers, health plans, and healthcare clearinghouses, that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek

attorneys' fees and costs associated with pursuing federal civil actions. In addition, many state laws govern the privacy and security of health information in specified circumstances. For example, in California the California Consumer Privacy Act (CCPA) establishes a new privacy framework for covered businesses by creating a broad definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. Many of the state laws differ from each other in significant ways and may have a more prohibitive effect than HIPAA and cover personal information other than protected health information that is subject to HIPAA, thus complicating compliance efforts.

We may develop products that, once approved, may be administered by a physician. Under currently applicable U.S. law, certain products not usually self-administered (including injectable drugs) may be eligible for coverage under Medicare through Medicare Part B. Medicare Part B is part of original Medicare, the federal health care program that provides health care benefits to the aged and disabled, and covers outpatient services and supplies, including certain pharmaceutical products, that are medically necessary to treat a beneficiary's health condition. As a condition of receiving Medicare Part B reimbursement for a manufacturer's eligible drugs, the manufacturer is required to participate in other government healthcare programs, including the Medicaid Drug Rebate Program and the 340B Drug Pricing Program. The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of HHS as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to entities that participate in the program.

In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors.

Additionally, the federal Physician Payments Sunshine Act, or the Sunshine Act, within the Affordable Care Act, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to CMS information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. In addition, many states also govern the reporting of payments or other transfers of value, many of which differ from each other in significant ways, are often not pre-empted, and may have a more prohibitive effect than the Sunshine Act, thus further complicating compliance efforts.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Ensuring business arrangements with third parties comply with applicable healthcare laws and regulations is a costly endeavor. If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other current or future governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, individual

imprisonment, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private "qui tam" actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other 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.

Coverage, pricing and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may obtain regulatory approval. In the United States and in foreign markets, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, such as Medicare and Medicaid, private managed care providers, health insurers and other organizations. Adequate coverage and reimbursement from third-party payors are critical to new product acceptance.

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 therapeutic 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.

We cannot be sure that reimbursement will be available for any product that we commercialize and, if coverage and reimbursement are available, what the level of reimbursement will be. Coverage may also be more limited than the purposes for which the product is approved by the FDA or comparable foreign regulatory authorities. Reimbursement may impact the demand for, or the price of, any product for which we obtain regulatory approval.

Third-party payors are increasingly challenging the price, examining the medical necessity, and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with branded drugs and drugs administered under the supervision of a physician. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. 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 product on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. A third-party payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, in the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors. Private third-party payors tend to follow Medicare coverage and reimbursement limitations to a substantial degree, but also have their own methods and approval process apart from Medicare determinations. Therefore, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize any product candidate that we successfully develop.

Different pricing and reimbursement schemes exist in other countries. In the European Union, or EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical

trials that compare the cost effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if third-party payors fail to provide coverage and adequate reimbursement. In addition, emphasis on managed care, the increasing influence of health maintenance organizations, and additional legislative changes in the United States has increased, and we expect will continue to increase, the pressure on healthcare pricing. The downward pressure on the rise in healthcare costs in general, particularly prescription medicines, medical devices and surgical procedures and other treatments, has become very intense. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare reform

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect the ability to profitably sell product candidates for which marketing approval is obtained. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Affordable Care Act has substantially changed healthcare financing and delivery by both governmental and private insurers. Among the Affordable Care Act provisions of importance to the pharmaceutical and biotechnology industries, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs that began in 2011;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively, and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70%, the current discount owed as of January 1, 2019 pursuant to the Bipartisan Budget Act of 2018, or BBA) point-of-sale discounts, off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals beginning in 2014 and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the 340B Drug Discount Program;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- expansion of healthcare fraud and abuse laws, including the FCA and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected;
- requirements to report certain financial arrangements with physicians and teaching hospitals;

- a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to physicians;
- establishment of the Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending; and
- a licensure framework for follow on biologic products._

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court, and the Trump Administration has issued various Executive Orders which eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Additionally, Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business, especially under the Biden administration.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the former Trump administration’s budget proposal for fiscal year 2021 included a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the former administration sent “principles” for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the former administration also previously released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS’s policy change that was effective January 1, 2019. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions after January 20, 2021.

In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that certain drug and biologic manufacturers can charge for medications sold to certain health care facilities. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any. On July 24, 2020 and September 13, 2020, former President Trump announced several executive orders related to prescription drug pricing that seek to implement several of the former administration's proposals. In response, the FDA released a final rule on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021 and ending December 31, 2027. However, in response to a lawsuit filed by several industry groups, on December 28, the U.S. District Court for the Northern District of California issued a nationwide preliminary injunction enjoining government defendants from implementing the MFN Rule pending completion of notice-and-comment procedures under the Administrative Procedure Act. On January 13, 2021, in a separate lawsuit brought by industry groups in the U.S. District of Maryland, the government defendants entered a joint motion to stay litigation on the condition that the government would not appeal the preliminary injunction granted in the U.S. District

Court for the Northern District of California and that performance for any final regulation stemming from the MFN Interim Final Rule shall not commence earlier than 60 days after publication of that regulation in the Federal Register. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the MFN Model may materially and adversely affect the price we receive for any of our product candidates. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to an order entered by the U.S. District Court for the District of Columbia, the portion of the rule eliminating safe harbor protection for certain rebates related to the sale or purchase of a pharmaceutical product from a manufacturer to a plan sponsor under Medicare Part D has been delayed to January 1, 2026. This deadline was delayed to January 1, 2027 by the Bipartisan Safer Communities Act. The Inflation Reduction Act of 2022 further delayed implementation of this rule to January 1, 2032. While a number of these and other proposed measures may require additional authorization to become effective, and the Biden administration may reverse or otherwise change these measures, Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to request access to certain investigational new drug products that have completed a Phase I 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 pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or 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 accounting provisions requiring us 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.

Government regulations outside the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products as well as authorization and approval of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the EU, for example, a Clinical Trial Application, or CTA, must be submitted for each clinical trial to each country's national competent authority, or NCA, and an independent ethics committee, or EC, much like the FDA and an IRB, respectively. Under the new Clinical Trials Regulation (EU) no 536/2014, which replaced the Clinical Trials Directive 2001/20/EC on January 31, 2022, a single application is now made through the Clinical Trials Information System, or CTIS, for clinical trial authorization in up to 30 EU/EEA countries at the same time and with a single set of documentation.

The assessment of applications for clinical trials, which is divided in two parts (Part I contains scientific and medicinal product documentation and Part II contains the national and patient-level documentation). Part I is assessed by a coordinated review by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned) of a draft report prepared by a Reference Member State. 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 EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation. The new Clinical Trials Regulation also provides for simplified reporting procedures for clinical trial sponsors.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Regulation in the European Union

In the EU, medicinal products are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. To obtain regulatory approval of a medicinal product in the EU, we must submit an MA application. The application used to submit the BLA in the United States is similar to that required in the EU, with certain exceptions. There are two main types of MA in the EU:

- The centralized MA is issued by the European Commission through the centralized procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the EMA, which is valid throughout the entire territory of the EU, and in the additional Member States of the European Economic Area (Iceland, Liechtenstein and Norway), or EEA. The centralized procedure is mandatory for certain types of products, including medicines produced by as biotechnological process, products as designated as orphan medicinal products, advanced-therapy medicinal products (i.e. gene-therapy, somatic cell-therapy or tissue-engineered medicines) and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EU, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU. Under the centralized procedure the maximum timeframe for the evaluation of an MA application by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Clock stops may extend the timeframe of evaluation of an MA application considerably beyond 210 days. Where the CHMP gives a positive opinion, the EMA provides the opinion together with supporting documentation to the European Commission, who make the final decision to grant an MA, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MA application under the accelerated assessment procedure is of 150 days, excluding clock stops, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment.
- National MAs, which are issued by the competent authorities of the Member States of the EU and only cover their respective territory, are available for products not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in a Member State of the EU, this national MA can be recognized in other Member States through the mutual recognition procedure. If the product has not received a national MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of product characteristics, or SmPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Concerned Member States, or CMSs) for their approval. If the CMSs raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the CMSs).

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EU make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Now that the UK (which comprises Great Britain and Northern Ireland) has left the EU, Great Britain is no longer covered by centralized MAs (under the Northern Ireland Protocol, centralized MAs continues to be recognized in Northern Ireland). All medicinal products with a centralized MA were automatically converted to Great Britain MAs on January 1, 2021. For a period of three years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, may rely on a decision taken by the European Commission on the approval of a new MA in the centralized procedure, in order to more quickly grant a new Great Britain MA. A separate application will, however, still be required. On January 24, 2023, the MHRA announced that a new international recognition framework will be put in place from January 1, 2024, which will have regard to decisions on the approval of MAs made by the European Medicine Agency and certain other regulators when determining an application for a new Great Britain MA. The MHRA also has the power to have regard to MAs approved in EU Member States through decentralized or mutual recognition procedures with a view to more quickly granting an MA in the United Kingdom or Great Britain.

The EU also provides opportunities for regulatory exclusivity. For example, in the EU, upon receiving an MA, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from referencing the innovator's preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU, during a period of eight years from the date on which the reference product was first authorized in the EU. During the additional two-year period of market exclusivity, a generic or biosimilar MA application can be submitted and authorized, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed in the EU until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are determined to bring a significant clinical benefit in comparison with currently approved therapies. There is no guarantee that a product will be considered by the EMA to be an innovative medicinal product, and products may not qualify for data exclusivity. Even if an innovative medicinal product gains the prescribed period of data exclusivity, another company could nevertheless also market another version of the product if such company obtained an MA based on an application with a complete and independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Pediatric development in the Europe Union

In the EU, companies developing a new medicinal product must agree upon a pediatric investigation plan, or PIP, with the EMA's Pediatric Committee, or PDCO, and must conduct pediatric clinical trials in accordance with that PIP, 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. 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 PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the product for which an MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when this data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Products that are granted an MA on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six-month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

PRIME designation

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, where the MA application will be made through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones. 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 MA application assessment once a dossier has been submitted. Importantly, a dedicated contact and rapporteur from the EMA's CHMP or Committee for Advanced Therapies are appointed early in 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. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

Post-approval controls in the European Union

The holder of an MA must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MA applications must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, or SmPC, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each EU Member State and can differ from one country to another.

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

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

Regulation of Combination Products

The EU regulates medical devices and medicinal products separately, through different legislative instruments, and the applicable requirements will vary depending on the type of drug-device combination product. EU guidance has been published to help manufacturers select the right regulatory framework. In the case of drug-delivery products intended to administer a medicinal product where the device and the medicinal product do not form a single integral product, the medicinal product is regulated in accordance with the aforementioned rules while the device part is regulated as a medical device and will have to comply with all the requirements set by Regulation 2017/745, or the Medical Devices Regulation (which became applicable on 26 May 2021 and repealed the EU Council Directive 93/42/EEC, or the Medical Devices Directive). Where the medical device and medicinal product form a single integrated product (e.g. pre-filled inhalers), if the principal intended action is achieved by the medicine, the product is considered a medicinal product that includes a medical device and the entire product is regulated under the EU pharmaceutical legislation. However, the MA application for the product should include a CE certificate for the device in accordance with the Medical Devices Regulation or, if not CE marked but would need to be certified if marketed separately, the applicant must include an opinion from a notified body on conformity of device (except for Class I non-sterile, non-measuring devices). This is a requirement under the new Medical Devices Regulation.

The characteristics of non-integral devices used for the administration of medicinal products may impact the quality, safety and efficacy profile of the medicinal products. To the extent that administration devices are co-packaged with the medicinal product or, in exceptional cases, where the use of a specific type of administration device is specifically provided for in the product information of the medicinal product, additional information may need to be provided in the MA application for the medicinal product on the characteristics of the medical device(s) that may impact on the quality, safety and/or efficacy of the medicinal product. The requirements regarding quality aspects for integral drug-device combination products, including devices that are co-packaged with medicinal products, are outlined in an EMA guideline which came into effect on January 1, 2022.

The EU requires that all medical devices placed on the market in the EU must meet the relevant general safety and performance requirements laid down in Annex I of the Medical Devices Regulation. The most fundamental requirement is that a medical device must be designed and manufactured in such a way that it will not compromise the clinical condition or safety of patients, or the safety and health of users and others. In addition, the device must achieve the performances intended by the manufacturer and be designed, manufactured, and packaged in a suitable manner. To demonstrate compliance with the general safety and performance requirements laid down in Annex I to the Medical Devices Regulation, medical device manufacturers must undergo a conformity assessment procedure, which varies according to the type of medical device and its (risk) classification. Conformity assessment procedures require an assessment of available clinical evidence, literature data for the product, and post-market experience in respect of similar products already marketed. Except for low-risk medical devices (Class I non-sterile, non-measuring devices), where the manufacturer can self-declare the conformity of its products with the general safety and performance requirements (except for any parts which relate to sterility or metrology), a conformity assessment procedure requires the intervention of a notified body. Notified bodies are independent organizations designated by EU countries to assess the conformity of devices before being placed on the market. If satisfied that the relevant product conforms to the relevant general safety and performance requirements, the notified body issues a certificate of conformity, which the manufacturer uses as a basis for its own declaration of conformity. The manufacturer may then apply the CE mark to the device, which allows the device to be placed on the market throughout the EU.

As a general rule, demonstration of conformity of medical devices and their manufacturers with the general safety and performance requirements must be based, among other things, on the evaluation of clinical data supporting the safety and performance of the products during normal conditions of use. Specifically, a manufacturer must demonstrate that the device achieves its intended performance during normal conditions of use, that the known and foreseeable risks, and any adverse events, are minimized and acceptable when weighed against the benefits of its intended performance, and that any claims made about the performance and safety of the device are supported by suitable evidence

The aforementioned EU rules are generally applicable in the EEA.

European data collection

The collection and use of personal health data in the EEA is governed by the General Data Protection Regulation, or GDPR, which became effective May 25, 2018. The GDPR imposes more stringent requirements relating to the consent of the individuals to whom the personal data relates, the information provided to the individuals, notification of data processing obligations to the competent national data protection authorities, and the security and confidentiality of the personal data. The GDPR also impose strict rules on the transfer of personal data out of the EU to the United States. Failure to comply with the requirements of the GDPR, and the related national data protection laws of the EEA Member States may result in fines and other administrative penalties. The GDPR introduces new data protection requirements in the EEA and substantial fines for breaches of the data protection rules, specifically fines are increased to levels of up to 4% total worldwide annual turnover or up to €20 million (whichever is higher). The GDPR regulations may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. We are subject to the GDPR if we have a presence or "establishment" in the EEA (e.g. EEA based subsidiary or operations), when conducting clinical trials with EEA based data subjects (whether the trials are conducted directly by us or through a clinical vendor or partner) or offering approved products or services (if relevant) to EEA based data subjects (regardless of whether involving our EEA based subsidiary or operations). The GDPR regulations may be onerous and adversely affect our business, financial condition, results of operations, and prospects.

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

Brexit and the Regulatory Framework in the United Kingdom

The UK formally left the EU on January 31, 2020 and the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not provide for wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework continues to apply in Northern Ireland). The regulatory regime in Great Britain therefore largely aligns with current EU regulations, however it is possible that these regimes will diverge more significantly in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation.

Rest of world regulation

For other countries outside the EU and the United States, such as countries in Eastern Europe, Latin America, Middle East, or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary from country to country. Additionally, the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions, or criminal prosecution.

Additional regulation

In addition to the foregoing, local, state and federal laws regarding such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations. We may incur significant costs to comply with such laws and regulations now or in the future.

Human Capital Resources

We believe the success of our mission largely depends on our ability to attract and retain highly skilled employees. We believe programs that foster company engagement, diversity, equity and inclusion, growth and development while providing competitive compensation and benefits will attract a diverse population of employees who will bring innovative ideas and creative solutions that will enable the achievement of our goals. Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards.

As of February 28, 2023, we employed 38 full-time employees, including 25 in research and development and 13 in general and administrative and one part-time employee. Seven of our employees hold M.D. or Ph.D. degrees. We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective-bargaining arrangements. We consider our employee relations to be good.

Corporate Information

We were incorporated under the laws of the state of Delaware on in January 2017 as Pippin Pharmaceuticals, Inc. On May 16, 2018, we changed our name to Akero Therapeutics, Inc. Our mailing address and executive offices are located at 601 Gateway Boulevard, Suite 350, South San Francisco, California 94080 and our telephone number at that address is (650) 487-6488. We maintain an Internet website at the following address: www.akerotx.com. The information on our website is not incorporated by reference in this Annual Report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

Available Information

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, exhibits and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.akerotx.com, under “Investors – Corporate Governance.”

The SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding us and other issuers that file electronically with the SEC. The SEC's Internet website address is http://www.sec.gov.

Item 1A. Risk Factors.

In evaluating the Company and our business, careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occur, our business, prospects, financial condition, results of operations and cash flow could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition, results of operations or cash flow.

Risks Related to the Clinical Development and Manufacturing of our Product Candidate

Risks Related to Clinical Development

Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control, including difficulties in identifying patients with NASH, significant competition for recruiting such patients in clinical trials, and restrictions on patients and investigators related to the ongoing COVID-19 pandemic.

Identifying and qualifying patients to participate in clinical trials is critical to our success. We may be unable to retain a sufficient number of patients to complete the ongoing Phase 2b SYMMETRY study, or be unable to retain a sufficient number of patients to successfully complete the long-term follow-up portion of the ongoing Phase 2b HARMONY study, and may encounter delays in enrolling or be unable to enroll or retain a sufficient number of patients in any of our future clinical trials. In particular, as a result of the inherent difficulties in diagnosing NASH and the significant competition for recruiting patients with NASH in clinical trials, there may be delays in enrolling the patients we need to complete clinical trials on a timely basis, or at all.

Factors that may generally affect patient enrollment include:

- the size and nature of the patient population;
- the number and location of clinical sites we enroll;
- the ability of our clinical sites to maintain adequate personnel;
- competition with other companies for clinical sites or patients;
- the eligibility and exclusion criteria for the trial;
- the design of the clinical trial;
- inability to obtain and maintain patient consents;
- risk that enrolled participants will drop out before completion; and
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating.

In addition, if any significant adverse events or other side effects are observed in any of our future clinical trials, it may make it more difficult for us to recruit patients to our clinical trials and patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of one or more product candidates altogether. Our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays, which would increase our costs and have an adverse effect on our company.

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

The biotechnology industry is intensely competitive and subject to rapid and significant technological change. Our competitors include multinational pharmaceutical companies, specialized biotechnology companies and universities and other research institutions. We understand that a number of pharmaceutical companies, including AstraZeneca PLC/MedImmune LLC, Boehringer Ingelheim AG, Bristol-Myers Squibb Company, Inc., Eisai, Inc., Eli Lilly, GSK plc, and Company, Johnson & Johnson, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Pfizer

Inc., Roche Holding AG, Sanofi and Takeda Pharmaceutical Company Limited, as well as large and small biotechnology companies such as Albireo Pharma, Inc., Alnylam Pharmaceuticals, Inc., Altimmune, Inc., Amgen, Inc., Arrowhead Pharmaceuticals, Inc., Axcella Health, Inc., Boston Pharmaceuticals, Inc., Cirius Therapeutics, Inc., CohBar, Inc., CymaBay Therapeutics, Inc., 89bio, D&D Pharmatech, Inc., Enanta Pharmaceuticals, Inc., Galectin Therapeutics Inc., Galmed Pharmaceuticals Ltd., Gilead Sciences, Inc., Hanmi Pharmaceutical Company, Ltd., Intercept Pharmaceuticals, Inc., Inventiva Pharma SA, Ionis Pharmaceuticals, Inc., Madrigal Pharmaceuticals, Inc., MediciNova, Inc., North Sea Pharmaceuticals, Poxel SA, Sagimet Biosciences, Inc., Terns Pharmaceuticals, Inc. and Viking Therapeutics, Inc. are or may be pursuing the development or marketing of pharmaceuticals that target NASH. It is also probable that the number of companies seeking to develop products and therapies for the treatment of serious metabolic diseases, such as NASH, will increase. Many of our competitors have substantially greater financial, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior products. In addition, many of these competitors have significantly greater experience than we have in undertaking nonclinical studies and human clinical trials of new pharmaceutical products and in obtaining regulatory approvals of human therapeutic products. Accordingly, our competitors may succeed in obtaining FDA approval for superior products. In addition, many competitors have greater name recognition and more extensive collaborative relationships.

Smaller and earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies.

Our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidate or any future product candidates. Our competitors may also develop drugs that are more effective, more convenient, more widely used and less costly or have a better safety profile than our products and these competitors may also be more successful than we are in manufacturing and marketing their products. If we are unable to compete effectively against these companies, then we may not be able to commercialize our product candidate or any future product candidates or achieve a competitive position in the market. This would adversely affect our ability to generate revenue. Our competitors also compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Failures or delays in the commencement or completion of, or ambiguous or negative results from our planned clinical trials of our product candidates could result in increased costs to us and could delay, prevent, or limit our ability to generate revenue and continue our business.

We do not know whether the long-term follow-up portion of the HARMONY study or the SYMMETRY study, including the expansion cohort known as Cohort D, will be completed or any future clinical trials will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- the FDA or comparable foreign regulatory authorities may not authorize us or our investigators to commence our planned clinical trials or any other clinical trials we may initiate, or may suspend our clinical trials, for example, through imposition of a clinical hold, and may request additional data to permit allowance of our IND;
- delays in filing or receiving allowance of additional INDs that may be required;
- lack of adequate funding to continue our clinical trials and nonclinical studies;
- negative results from our ongoing nonclinical studies;
- delays in reaching or failing to reach agreement on acceptable terms with prospective clinical research organizations, or CROs, and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and study sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials, for example delays in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining ethics committee or Institutional Review Board, or IRB, approval to conduct a clinical study at a prospective site or sites;
- challenges in recruiting and enrolling subjects to participate in clinical trials, the proximity of subjects to study sites, eligibility criteria for the clinical study, the nature of the clinical study protocol, the availability of approved effective treatments for the relevant disease, and competition from other clinical study programs for similar indications;

- severe or unexpected drug-related side effects experienced by subjects in a clinical trial;
- we may decide, or regulatory authorities may require us, to conduct additional nonclinical or clinical trials or abandon product development programs;
- delays in validating, or inability to validate, any endpoints utilized in a clinical trial;
- the FDA or comparable foreign regulatory authorities may disagree with our clinical study design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;
- difficulties retaining subjects who have enrolled in a clinical trial but may be prone to withdrawal due to rigors of the clinical trials, lack of efficacy, side effects, personal issues, or loss of interest; and
- the impact of COVID-19 on the initiation or completion of clinical trials or the reporting of results of our clinical trials and the supply of our product candidate.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical study may be suspended or terminated by us, the FDA or comparable foreign regulatory authorities, the IRBs at the sites where the IRBs are overseeing a clinical study, a data and safety monitoring board, or DSMB, overseeing the clinical study at issue or other regulatory authorities due to a number of factors, including, among others:

- failure to conduct the clinical study in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical study operations or study sites by the FDA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including in response to the imposition of a clinical hold;
- unforeseen safety issues or safety signals, including any that could be identified in our ongoing nonclinical studies or clinical trials, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical supply materials; and
- lack of adequate funding to continue clinical trials.

Any inability to successfully complete nonclinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make changes to a product candidate, such as the recently developed drug product-device combination that we plan to use in Phase 3 clinical trials, we may need to conduct additional nonclinical studies or clinical trials to bridge or demonstrate the comparability of our modified product candidate to earlier versions, which could delay our clinical development plan or marketing approval for our current product candidate and any future product candidates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

Clinical development is uncertain and our clinical trials for EFX and any future product candidates may experience delays, which would adversely affect our ability to obtain regulatory approvals or commercialize these programs on a timely basis or at all, which would have an adverse effect on our business.

We cannot be sure that we will be able to continue development of EFX or submit INDs or similar applications for any future product candidates, on the timelines we expect, if at all. To proceed with our development plans and ultimately commercialization, we may need to conduct and meet regulatory requirements for additional preclinical studies and clinical trials. We cannot be certain of the timely completion or outcomes of our preclinical testing and studies and cannot predict if the FDA or other regulatory authorities will accept our proposed clinical programs or if the outcomes of our preclinical studies and clinical trials will enable any future clinical trials to begin under a proposed protocol.

We rely and will continue to rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize any potential product candidates.

We depend and will continue to depend upon third parties, including independent investigators, to conduct our clinical trials under agreements with universities, medical institutions, CROs, strategic partners and others. We expect to

have to negotiate budgets and contracts with CROs and trial sites, which may result in delays to our development timelines and increased costs.

We rely heavily on third parties over the course of our clinical trials, and, as a result, have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to their compliance with the approved clinical protocol. Nevertheless, our reliance on third parties does not relieve us of our regulatory responsibilities and we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards. We and these third parties are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of these third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to suspend or terminate these trials or perform additional nonclinical studies or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, regulatory authorities will determine that any of our clinical trials comply with the GCP requirements. In addition, our clinical trials must be conducted with products produced under current good manufacturing practice, or cGMP, requirements and may require a large number of patients. Our failure or any failure by these third parties to comply with these applicable regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

The third parties who conduct our clinical trials are not our employees and, except for remedies that may be available to us under our agreements with those third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing nonclinical and clinical programs. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, such as due to the impacts of COVID-19, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates in a timely manner or at all. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into arrangements with alternative CROs or other third parties or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines due to the impact of COVID-19 or for other reasons or if the quality or accuracy of the clinical data they obtain is compromised due to the failure (including by clinical sites or investigators) to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase substantially and our ability to generate revenues could be delayed significantly.

Risks Related to the Manufacturing of our Product Candidate

We are subject to many manufacturing risks, any of which could substantially increase our costs, delay clinical programs and limit supply of our products.

We have contracted with a third-party manufacturer, Boehringer Ingelheim, to make EFX drug substance (active pharmaceutical ingredient, or API) and with another third-party manufacturer, Vetter Pharma International GmbH, or Vetter, to manufacture EFX drug product, or DP, including a DP-device combination to be used in Phase 3 studies. We have successfully manufactured API and a DP-device combination under GMP conditions, which have both been released for Phase 3 clinical use. We plan to enter into new commercial supply agreements with each of Boehringer Ingelheim and Vetter at the appropriate time. Even though the GMP DP being used for our ongoing HARMONY study is similar to the DP that was used for the BALANCED study, which is stored as a frozen liquid until immediately before administration to trial subjects, the process of manufacturing our product is complex, highly regulated and subject to several risks, including:

- the manufacturing process is susceptible to product loss due to contamination by adventitious microorganisms, equipment failure, improper installation or operation of equipment, vendor or operator error and improper storage conditions. Even minor deviations from normal manufacturing processes could result in reduced production yields and quality as well as other supply disruptions. If microbial, viral, including COVID-19, or other contaminations are discovered in our products or in the manufacturing facilities in which our products are made, the manufacturing facilities may need to be closed for an extended period of time to investigate and eliminate the contamination;
- the manufacturing facilities in which our products are made could be adversely affected by equipment failures, labor and raw material shortages, pandemics, epidemics, or outbreaks of infectious disease, financial difficulties of our contract manufacturers, natural disasters, power failures, local political unrest and numerous other factors; and
- any adverse developments affecting manufacturing operations for our products may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls or other interruptions in the supply of our products. We may also have to record inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek more expensive manufacturing alternatives.

The manufacture of EFX requires significant expertise and capital investment, including the development of advanced manufacturing techniques and in-process controls. Manufacturers of these products sometimes encounter difficulties in production, especially during scale-up from the manufacturing process used for early clinical trials to a validated and qualified process needed for pivotal clinical trials and commercial launch. These problems include failure to meet target production costs and yields, failure to meet product release specifications, including stability of the product, quality assurance system failures, operator error and shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot assure you that any product quality issues relating to the manufacture of our product candidate or any future product candidates will not occur in the future.

We do not have, and we do not currently plan to acquire or build the facilities or internal capabilities to manufacture bulk drug substance, finished drug product or delivery device for use in clinical trials or commercialization. To a large extent, that makes us dependent on the goodwill of our contract manufacturing partners to quickly fix deviations that will inevitably occur during the manufacturing of our product. Any delay or interruption in the supply of clinical trial materials, including on account of the impact of the COVID-19 pandemic on our contract manufacturing partners, could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials altogether.

We have developed a new lyophilized, drug product formulation of EFX for use in Phase 3 clinical trials and, if EFX is approved, for commercialization. This formulation was developed under contract with a specialist formulation development company, Coriolis Pharma Research GmbH. We have contracted with Vetter to manufacture this formulation as a dual-chamber, pre-filled syringe combination product for use in Phase 3 clinical trials. Scale-up of manufacturing at Vetter and release of clinical batches has been completed. However, we must still demonstrate comparable exposure between the formulation used in Phase 2 clinical trials and the new DP-device combination planned for use in Phase 3. There is no assurance that we will be successful in completing this development on a timely

basis, including accounting for any impact of the COVID-19 pandemic, or at all, which could impede our development and commercialization strategy for EFX. Further, the FDA or other similar foreign regulatory bodies could require nonclinical studies or clinical trials to support introduction of any new formulation or its presentation as a drug-device combination product, which could increase our development costs and delay or prevent us from proceeding with future clinical trials or commercialization of EFX, if approved.

We contract with third parties for the manufacture of EFX and the delivery device utilized for EFX and expect to continue to do so for future clinical trials and for commercialization of EFX as well as for any future product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of EFX, or the delivery devices utilized for EFX, or any future product candidates or medicines or that such supply will not be available to us at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of EFX, delivery devices utilized for EFX or any future product candidates for nonclinical and clinical testing and for commercial supply of any of these product candidates for which we obtain marketing approval. Reliance on third-party manufacturers may expose us to different risks than if we were to manufacture product candidates ourselves. To the extent any issues arise with our third-party manufacturers, we may be unable to establish any agreements with any other 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:

- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance and safety and pharmacovigilance reporting.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. For our product candidates that are biologic-device combination products, third-party manufacturers may not be able to comply with cGMP regulatory requirements applicable to biologic-device combination products, including applicable provisions of the FDA's drug product cGMP regulations, device cGMP requirements embodied in the FDA's Quality System Regulation, or QSR, or similar regulatory requirements outside the United States. Our failure, or the failure of third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations.

If any CMO with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different CMO, which we may not be able to do on reasonable terms, if at all. In either scenario, our clinical trials supply could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our product candidates may be unique or proprietary to the original CMO and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change CMOs for any reason, we will be required to verify that the new CMO maintains facilities and procedures that comply with quality standards and with all applicable regulations. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product candidate according to the specifications previously submitted to or approved by the FDA or another regulatory authority. The delays associated with the verification of a new CMO could negatively affect our ability to develop product candidates or commercialize our products in a timely manner or within budget. Furthermore, a CMO may possess technology related to the manufacture of our product candidate that such CMO owns independently. This would increase our reliance on such CMO or require us to obtain a license from such CMO in order to have another CMO manufacture our product candidates. In addition, in the case of CMOs that supply our product candidate, changes in manufacturers often involve changes in manufacturing procedures and processes, which could require that we conduct bridging studies between our prior clinical supply used in our clinical trials and that of any new manufacturer. We may be unsuccessful in demonstrating the comparability of clinical supplies which could

require the conduct of additional clinical trials. Any medicines that we may develop may compete with other product candidates and products for access to manufacturing facilities. 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, such as delays in performance due to the ongoing COVID-19 pandemic, could delay clinical development or marketing approval. We are also unable to predict how the ongoing COVID-19 pandemic may affect our third-party manufacturers, including any potential disruptions to our global supply chain. We do not currently have arrangements in place for redundant supply of bulk drug substance or for the manufacture of our drug product-delivery device combination. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there potentially are alternative manufacturers who could manufacture our drug substance or drug product-delivery device combination or any future product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

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

The manufacture of our product candidates is complex and we may encounter difficulties in production. If we or any of our third-party manufacturers encounter such difficulties, or fail to meet rigorously enforced regulatory standards, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

The processes involved in manufacturing our product candidates, including pre-filled, dual-chamber syringe presentations of our product candidates, are complex, expensive, highly regulated, and subject to multiple risks. Further, as product candidates are developed through nonclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

In addition, the manufacturing process for any products that we may develop is subject to FDA and other comparable foreign regulatory authority approval processes and continuous oversight, and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements, including, for example, complying with cGMPs, applicable product tracking and tracing requirements and applicable QSRs, on an ongoing basis. If we or our third-party manufacturers are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our contract manufacturers will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging or comparability nonclinical or clinical trials or the repetition of one or more clinical trials, increase clinical study costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations, and growth prospects.

Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume pre-pandemic levels of inspection activities, including routine surveillance, bioresearch monitoring and pre-approval inspections. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the ongoing COVID-19 pandemic and may experience delays in their regulatory activities.

Risks Related to Our Business, Industry and Intellectual Property

Risks Related to Business Development

We are heavily dependent on the success of EFX, our only product candidate.

We currently have no products that are approved for commercial sale and may never be able to develop marketable products. We expect that a substantial portion of our efforts and expenditures over the next several years will be devoted to EFX, which is currently our only product candidate. Accordingly, our business currently depends heavily on the successful development, regulatory approval, and commercialization of EFX. We cannot be certain that EFX will receive regulatory approval or be successfully commercialized even if we receive regulatory approval. If we were required to discontinue development of EFX or if EFX does not receive regulatory approval or fails to achieve significant market acceptance, we would be delayed by many years in our ability to achieve profitability, if ever.

The research, testing, manufacturing, safety, efficacy, labeling, approval, sale, marketing, and distribution of EFX is, and will remain, subject to comprehensive regulation by the FDA and foreign regulatory authorities. Failure to obtain regulatory approval for EFX in the United States, Europe, Japan or other jurisdictions will prevent us from commercializing and marketing EFX in such jurisdictions.

Clinical development of EFX prior to the BALANCED study was conducted by Amgen, Inc., or Amgen, in patients with T2D. We did not conduct any of the development of EFX related to clinical trials in patients with T2D, and we have relied on Amgen to have conducted such research and development in accordance with the applicable protocol, legal, regulatory, and scientific standards, have accurately reported the results of all nonclinical studies and clinical trials conducted prior to our license of EFX, and have correctly collected and interpreted the data from these studies and trials. To the extent any of the foregoing has not occurred, our expected development time and development costs for EFX may be increased.

Even if we were to successfully obtain approval from the FDA and foreign regulatory authorities for EFX, any approval might contain significant limitations related to use, including limitations on the stage of disease EFX is approved to treat, as well as restrictions for specified age groups, warnings, precautions or contraindications. Furthermore, even if we obtain regulatory approval for EFX, we will still need to develop a commercial infrastructure or develop relationships with collaborators to commercialize, establish a commercially viable pricing structure and obtain coverage and adequate reimbursement from third-party payors, including government healthcare programs. If we, or any future collaborators, are unable to successfully commercialize EFX, we may not be able to generate sufficient revenue to continue our business.

We have expended and will continue to expend our limited resources to pursue a particular therapeutic candidate or indication, such as our focus on developing EFX for the treatment of NASH, and may fail to capitalize on therapeutic candidates or indications that may be more profitable or for which there is a greater likelihood of success.

We have focused our extensive research and development efforts on EFX for the treatment of NASH. Therefore, we have, and in the future may, forego or delay pursuit of opportunities with other therapeutic candidates or for other indications that later prove to have greater commercial potential. We are highly dependent on the success of the future clinical trials of EFX, the outcomes of which are uncertain. Because EFX is our first and only therapeutic candidate, if it encounters safety, efficacy, supply or manufacturing problems, developmental delays, regulatory or commercialization issues or other problems, the value of our platform could be greatly diminished and our development plans could be curtailed and our business would be significantly harmed.

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 EFX for the treatment of NASH may not yield any commercially viable therapeutic candidates. If we do not accurately evaluate the commercial potential or target market for a particular therapeutic candidate or misread trends in the biopharmaceutical industry, in particular for serious metabolic diseases, we may relinquish valuable rights to that therapeutic 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 therapeutic candidate.

At any time and for any reason, we may determine that one or more of our discovery programs or pre- clinical or clinical therapeutic candidates or programs does not have sufficient potential to warrant the allocation of resources toward such program or therapeutic candidate. Accordingly, we may choose not to develop a potential therapeutic candidate or elect to suspend, deprioritize or terminate one or more of our discovery programs or preclinical or clinical therapeutic candidates or programs. Suspending, deprioritizing or terminating a program or therapeutic candidate in which we have invested significant resources, means we will have expended resources on a program that will not provide a full return on our investment and may have missed the opportunity to have allocated those resources to potentially more productive uses, including existing or future programs or therapeutic candidates.

If we fail to develop and successfully commercialize other product candidates, our business and future prospects may be harmed and our business will be more vulnerable to any problems that we encounter in developing and commercializing our product candidate.

Our product candidate and any future product candidates must undergo rigorous clinical trials and regulatory approvals, and success in nonclinical studies or earlier-stage clinical trials may not be indicative of results in future clinical trials. EFX and any future product candidates will be subject to rigorous and extensive clinical trials and extensive regulatory approval processes implemented by the FDA and similar regulatory bodies in other jurisdictions. The approval process is typically lengthy and expensive, and approval is never certain. As a company, our only experience with clinical trials is our recently completed BALANCED study, our ongoing HARMONY study, for which we recently reported Week 24 results, and our ongoing SYMMETRY study, and we have not yet completed the clinical trials required to obtain regulatory approval. We may not be able to conduct clinical trials at preferred sites, enlist clinical investigators, enroll sufficient numbers of participants or begin or successfully complete clinical trials in a timely fashion, such as on account of the COVID-19 pandemic, if at all. Our anticipated clinical trials may be insufficient to demonstrate that our potential products will be active, safe or effective. Additional clinical trials may be required if clinical trial results are negative or inconclusive, which will require us to incur additional costs and significant delays.

Success in nonclinical studies and earlier-stage clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the effectiveness and safety of a product candidate. In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We may be unable to design and execute a clinical trial to support regulatory approval for a NASH therapy. In addition, there is a high failure rate for drugs and products proceeding through clinical trials. In fact, many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in nonclinical studies and earlier-stage clinical trials. Similarly, the outcome of nonclinical studies may not predict the success of clinical trials. Moreover, data obtained from nonclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product development. Additionally, we are developing a pre-filled, dual-chamber syringe presentation of EFX that is considered to be a biologic-device combination product by the FDA, and any BLA for EFX will require review and coordination by FDA's drug and device centers prior to approval. Any such delays could negatively impact our business, financial condition, results of operations and prospects. From time to time, we may publish interim ''top-line'' or preliminary data from our clinical trials. Preliminary or interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or interim data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could significantly harm our business and financial prospects.

In addition, certain of our hypotheses regarding the potential clinical and therapeutic benefit of EFX compared to other candidates in development for NASH are based on cross-trial comparisons of results that were not derived from head-to-head preclinical studies or clinical trials. These observations, which do not reflect robust comparative analyses, may suggest misleading similarities or differences due to differences in study protocols, conditions and patient

populations, and may not be reliable predictors of the relative efficacy or other benefits of EFX compared to other product candidates that are in development for the treatment of NASH.

We may develop EFX, and potentially future product candidates, in combination with other therapies, which exposes us to additional risks.

We may develop EFX and future product candidates in combination with one or more approved therapies. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA or similar regulatory authorities outside of the United States could revoke approval of the therapy used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues could arise with these existing therapies. This could result in our own products being removed from the market or being less successful commercially.

We may also evaluate EFX or any other future product candidates in combination with one or more other therapies that have not yet been approved for marketing by the FDA or similar regulatory authorities outside of the United States. We will not be able to market and sell EFX or any product candidate we develop in combination with any such unapproved therapies that do not ultimately obtain marketing approval. If the FDA or similar regulatory authorities outside of the United States do not approve these other drugs or revoke their approval, or if safety, efficacy, manufacturing, or supply issues arise with the drugs we choose to evaluate in combination with EFX or any other product candidate we develop, we may be unable to obtain approval of or market EFX or any other product candidate we develop.

If we are not successful in discovering, developing, receiving regulatory approval for and commercializing EFX and any future product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

Although we plan to devote a majority of our resources to the continued nonclinical and clinical testing and potential approval of EFX for the treatment of patients with NASH, another key element of our strategy is to discover, develop and commercialize a portfolio of products. We are seeking to do so through the identification and potential development of additional pipeline programs, but our resources are limited, and those that we have are geared towards nonclinical and clinical testing and seeking regulatory approval of EFX for the treatment of patients with NASH. We may also explore strategic collaborations for the development or acquisition of new product candidates, but we may not be successful in entering into such relationships. EFX is our only product candidate in clinical stages of development. Research programs to identify product candidates require substantial technical, financial and human resources, regardless of whether any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including:

- the research methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete;
- product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may, on further study, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- an approved product may not be accepted as safe and effective by trial participants, the medical community or third-party payors; and
- intellectual property or other proprietary rights of third parties for product candidates we develop may potentially block our entry into certain markets or make such entry economically impracticable.

Risks Related to our License and Third-Parties

We may be required to make significant payments under our license agreement for EFX.

We acquired worldwide, exclusive rights to EFX pursuant to our license agreement with Amgen, which we refer to as the Amgen Agreement. Under the Amgen Agreement, in consideration for the license, we made an upfront payment of $5.0 million to Amgen and also issued 2,653,333 shares of our Series A convertible preferred stock to Amgen at the time of the initial closing of our Series A Preferred Stock financing in June 2018, with a subsequent 3,205,128 shares of our Series A convertible preferred stock issued at the time of the second closing of the Series A Preferred Stock financing in November 2018. On July 2, 2019, we announced the dosing of the first patient in the BALANCED study of EFX, which resulted in a $2.5 million milestone obligation under the Amgen Agreement. As additional consideration for the license, we are required to pay Amgen $7.5 million in connection with dosing the first patient in a Phase 3 clinical trial, up to $30.0 million in connection with marketing approvals and aggregate milestone payments of up to $75.0 million upon the achievement of specified commercial milestones. Commencing on the first commercial sale of licensed products, we are obligated to pay tiered royalties of low to high single-digit percentages on annual net sales of the products covered by the license. If milestone or other non-royalty obligations become due, we may not have sufficient funds available to meet our obligations, which will materially adversely affect our business operations and financial condition.

If we breach our license agreement with Amgen related to EFX, we could lose the ability to continue the development and commercialization of EFX.

We are dependent on patents, know-how and proprietary technology in-licensed from Amgen. Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidate or any future product candidates and use our and our licensor's proprietary technologies without infringing the proprietary rights of third parties. Amgen may have the right to terminate the license agreement in full in the event we materially breach or default in the performance of any of the obligations under the license agreement. A termination of the license agreement with Amgen could result in the loss of significant rights and could harm our ability to commercialize our product candidates.

Disputes may also arise between us and Amgen, as well as any future potential licensors, regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidate and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

In addition, the Amgen Agreement under which we currently license intellectual property is complex, and certain provisions 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 increase what we believe to be our financial or other obligations under the Amgen 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 arrangement on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

We are generally also subject to all of the same risks with respect to protection of intellectual property that we license, as we are for intellectual property that we own, which are described below. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize products could suffer.

We may seek to establish collaborations, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

We may pursue collaborations in order to develop and commercialize EFX and any future product candidates. We face significant competition in seeking appropriate collaborators. 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 or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products and the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborators may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate 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 increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we may not be able to further develop our product candidate or any future product candidates or bring them to market and generate product revenue.

Risks Related to Employee Matters and Growth

We must attract and retain highly skilled employees in order to succeed. If we are not able to retain our current senior management team and our scientific advisors or continue to attract and retain qualified scientific, technical and business personnel, our business will suffer.

To succeed, we must recruit, retain, manage and motivate qualified clinical, scientific, technical and management personnel and we face significant competition for experienced personnel. If we do not succeed in attracting and retaining qualified personnel, particularly at the management level, it could adversely affect our ability to execute our business plan and harm our operating results. We are dependent on the members of our management team and our scientific advisors for our business success. We do not maintain "key person" insurance for any of our key personnel. An important element of our strategy is to take advantage of the research and development expertise of our current management and to utilize the expertise of our scientific advisors in the NASH field. We currently have employment agreements with all of our executive officers. Our employment agreements with our executive officers are terminable by them without notice and some provide for severance and change in control benefits. The loss of any one of our executive officers or key scientific consultants could result in a significant loss in the knowledge and experience that we, as an organization, possess and could cause significant delays, or outright failure, in the development and further commercialization of our product candidate or any future product candidates.

There is intense competition for qualified personnel, including management, in the technical fields in which we operate, and we may not be able to attract and retain qualified personnel necessary for the successful research, development and commercialization of EFX or any future product candidates. In particular, we have experienced a very competitive hiring environment in the San Francisco Bay Area, where we are headquartered. Many of the other pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources,

different risk profiles and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are unable to continue to attract and retain high-quality personnel, the rate and success with which we can discover and develop product candidates and our business will be limited.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We cannot ensure that our compliance controls, policies, and procedures will in every instance protect us from acts committed by our employees, agents, contractors, or collaborators that would violate the law or regulation, including, without limitation, healthcare, employment, foreign corrupt practices, environmental, competition, and patient privacy and other privacy laws and regulations. Such improper actions could subject us to civil or criminal investigations, and monetary and injunctive penalties, and could adversely impact our ability to conduct business, operating results, and reputation.

We are exposed to the risk of employee fraud or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to comply with the laws enforced by the FDA and other similar foreign regulatory bodies, fails to provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies, fails to comply with manufacturing standards we have established, fails to comply with healthcare fraud and abuse laws in the United States and similar foreign laws, or fails to report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under these laws will increase significantly, and our costs associated with compliance with these laws are also likely to increase. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. 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, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. 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 result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, and the curtailment or restructuring of our operations.

We may encounter difficulties in managing our growth, which could adversely affect our operations.

As of February 28, 2023, we had 38 full-time employees and one part-time employee. As we continue development and pursue the potential commercialization of EFX and other product candidates, as well as function as a public company, we will need to expand our financial, development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties. Our future financial performance and our ability to develop and commercialize our product candidate and to compete effectively will depend, in part, on our ability to manage any future growth effectively.

We may acquire additional technology and complementary businesses in the future. Acquisitions involve many risks, any of which could materially harm our business, including the diversion of management’s attention from core business concerns, failure to effectively exploit acquired technologies, failure to successfully integrate the acquired business or realize expected synergies or the loss of key employees from either our business or the acquired businesses.

Risks Related to Protecting Our Intellectual Property

Our success depends upon our ability to obtain and maintain intellectual property protection for our products and technologies. It is difficult and costly to protect our proprietary rights and technology, and we may not be able to ensure their protection.

Our success will depend in significant part on our and our current or future licensors', licensees' or collaborators' ability to establish and maintain adequate protection of our intellectual property covering the product candidates we plan to develop, and the ability to develop these product candidates and commercialize the products resulting therefrom, without infringing the intellectual property rights of others. We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking patents intended to cover our products and compositions, their methods of use, and any other inventions that are important to the development of our business. In addition to taking other steps to protect our intellectual property, we have applied for, and intend to continue to apply for, patents with claims covering our technologies, processes and product candidates when and where we deem it appropriate to do so. Our in-licensed patents and patent applications in both United States and certain foreign jurisdictions relate to EFX and related Fc-fusion polypeptides. There can be no assurance that the claims of our patents or any patent application that issues as a patent, will exclude others from making, using or selling our product candidate or any future product candidates or products that are substantially similar to our product candidate or any future product candidates. 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. In countries where we have not and do not seek patent protection, third parties may be able to manufacture and sell our product candidate or any future product candidates without our permission, and we may not be able to stop them from doing so.

With respect to patent rights, we do not know whether any of the pending patent applications for our product candidate or any future product candidates will result in the issuance of patents that effectively protect our technologies, processes and product candidates, or if any of our issued patents or our current or future licensors', licensees' or collaborators' issued patents will effectively prevent others from commercializing competitive technologies, processes and products. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or in some cases not at all, until they are issued as a patent. Therefore, we cannot be certain that we or our current or future licensors, licensees or collaborators were the first to make or file on the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our current or future licensors, licensees or collaborators were the first to file for patent protection of such inventions. There is also no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which could be used by a third party to challenge the validity of our patents, should they issue, or prevent a patent from issuing from a pending patent application. Any of the foregoing could harm our competitive position, business, financial condition, results of operations, and prospects.

Any changes we make to our product candidate or any future product candidates, including formulations that may be required for commercialization, or that cause them to have what we view as more advantageous properties may not be covered by our existing patents and patent applications, and we may be required to file new applications and/or seek other forms of protection for any such altered product candidates. The patent landscape surrounding the technology underlying our product candidate or any future product candidates is crowded, and there can be no assurance that we would be able to secure patent protection that would adequately cover an alternative to our product candidate or any future product candidates.

The patent prosecution process is expensive and time-consuming, and we and our current or future licensors, licensees or collaborators may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we or our current or future licensors, licensees or collaborators will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Moreover, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering technology that we license from or license to third parties and may be reliant on our current or future licensors, licensees or collaborators to perform these activities, which means that these patent applications may not be prosecuted, and these patents enforced, in a manner consistent with the best interests of our business. If our current or future licensors, licensees or collaborators fail to establish, maintain, protect or enforce such patents and other intellectual property rights, such rights may be reduced or eliminated. If our current or future licensors, licensees or

collaborators are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised.

The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, which in recent years have been the subject of much litigation, and, therefore, the issuance, scope, validity, enforceability, and commercial value of any patent claims that we have rights or may obtain cannot be predicted with certainty. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. 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 or narrow the scope of our patent protection. As a result, the issuance, scope, validity, enforceability and commercial value of our and our current or future licensors', licensees' or collaborators' patent rights are highly uncertain. Our and our current or future licensors', licensees' or collaborators' pending and future patent applications may not result in patents being issued that protect our technology or product candidates, or products resulting therefrom, in whole or in part, or that effectively prevent others from commercializing competitive technologies and products. The patent examination process may require us or our current or future licensors, licensees or collaborators to narrow the scope of the claims of pending and future patent applications, which would limit the scope of patent protection that is obtained, if any. Our and our current or future licensors', licensees' or collaborators' patent applications cannot be enforced against third parties practicing the technology that is currently claimed in such applications unless and until a patent issues from such applications, and then only to the extent the claims that issue are broad enough to cover the technology being practiced by third parties.

Furthermore, 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 the resulting products are commercialized. As a result, our owned and in-licensed patents may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. We expect to seek extensions of patent terms for our issued patents, where available. This includes in the United States under the Hatch-Waxman Act, which permits a patent term extension of up to five years beyond the original expiration date of the patent as compensation for regulatory delays. However, such a patent term extension cannot lengthen the remaining term of a patent beyond a total of 14 years from the product's approval date. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent and within 60 days of product approval. During the period of patent term extension, the claims of a patent are not enforceable for their full scope but are instead limited to the scope of the approved product. In addition, the applicable authorities, including the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. In addition, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to the expiration of relevant patents or otherwise failing to satisfy applicable requirements. If this occurs, any period during which we have the right to exclusively market our product will be shorter than we would otherwise expect, and our competitors may obtain approval of and launch products earlier than might otherwise be the case.

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

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. A number of U.S. patents directed to various aspects of EFX will expire in 2029; we currently anticipate that a composition of matter patent will be eligible for patent term extension to 2034. Even if patents covering our product candidate or any future product candidate are obtained, once the patent life has expired, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidate or any future product candidate might expire before or shortly after we or our partners commercialize those candidates. 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.

We may not be able to protect our intellectual property rights throughout the world.

The legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective or effective as that in the United States and we may, therefore, be unable to acquire and enforce intellectual property rights outside the United States to the same extent as in the United States. Whether filed in the United States or abroad, our patent applications may be challenged or may fail to result in issued patents.

In addition, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing or commercializing competing products. Furthermore, others may independently develop or commercialize similar or alternative technologies or drugs, or design around our patents. Our patents may be challenged, invalidated, circumvented or narrowed, or fail to provide us with any competitive advantages. In many foreign countries, patent applications and/or issued patents, or parts thereof, must be translated into the native language. If our patent applications or issued patents are translated incorrectly, they may not adequately cover our technologies; in some countries, it may not be possible to rectify an incorrect translation, which may result in patent protection that does not adequately cover our technologies in those countries.

Filing, prosecuting, enforcing and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States are less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and certain state laws in the United States. Consequently, we and our licensor may not be able to prevent third parties from practicing our and our licensor's inventions in all countries outside the United States, or from selling or importing products made using our and our licensor's inventions in and into the United States or other jurisdictions. Competitors may use our and our licensor's 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 and our licensor have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidate or any future product candidates and our and our licensor's 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 and other intellectual property protection, particularly those relating to biotechnology. This could make it difficult for us and our licensor to stop the infringement of our and our licensor's patents or the marketing of competing products in violation of our and our licensor's proprietary rights, generally. Proceedings to enforce our and our licensor's patent rights in foreign jurisdictions could result in substantial costs and divert our and our licensor's efforts and attention from other aspects of our business, could put our and our licensor's patents at risk of being invalidated or interpreted narrowly, could place our and our licensor's patent applications at risk of not issuing and could provoke third parties to assert claims against us or our licensor. We or our licensor may not prevail in any lawsuits that we or our licensor initiate and the damages or other remedies awarded, if any, may not be commercially meaningful.

The requirements for patentability differ in certain countries, particularly developing countries. For example, China has a heightened requirement for patentability and, specifically, requires a detailed description of medical uses of a claimed drug. In addition, India, certain countries in Europe and certain developing countries, including Thailand, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we and our licensor may have limited remedies if patents are infringed or if we or our licensor are compelled to grant a license to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. 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. Accordingly, our and our licensor's efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance and annuity fees on issued United States patents and most foreign patent applications and patents must be paid to the U.S. Patent and Trademark Office, or USPTO, and foreign patent agencies, respectively, in

order to maintain such 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, examination and issuance processes. While an inadvertent lapse can, in some 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. If we or our licensor fail to maintain the patents and patent applications covering our product candidate or any future product candidates, our competitors might be able to enter the market with similar or identical products or technology, which would have a material adverse effect on our business, financial condition and results of operations.

We may be unable to obtain intellectual property rights or technology necessary to develop and commercialize EFX or any future product candidates.

Several third parties are actively researching and seeking and obtaining patent protection in the NASH field, and there are issued third-party patents and published third-party patent applications in these fields. However, we may not be aware of all third-party intellectual property rights potentially relating to our product candidate or any future product candidates and technologies.

Depending on what patent claims ultimately issue and how courts construe the issued patent claims, as well as depending on the ultimate formulation and method of use of our product candidate or any future product candidates, we may need to obtain a license under such patents. There can be no assurance that such licenses will be available on commercially reasonable terms, or at all. If a third party does not offer us a necessary license or offers a license only on terms that are unattractive or unacceptable to us, we might be unable to develop and commercialize one or more of our product candidate or any future product candidates, which would have a material adverse effect on our business, financial condition and results of operations. Moreover, even if we obtain licenses to such intellectual property, but subsequently fail to meet our obligations under our license agreements, or such license agreements are terminated for any other reasons, we may lose our rights to in-licensed technologies.

The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue 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.

Our inability to protect our confidential information and trade secrets would harm our business and competitive position.

In addition to seeking patents for some of our technology and products, in our activities we also rely substantially on trade secrets, including unpatented know-how, technology and other proprietary materials and information, to maintain our competitive position. We seek to protect these trade secrets, 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, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. However, these steps may be inadequate, we may fail to enter into agreements with all such parties or any of these parties may breach the agreements and disclose our proprietary information and there may be no adequate remedy available for such breach of an agreement. We cannot assure you that our proprietary information will not be disclosed or that we can meaningfully protect our trade secrets. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts both within and outside the United States may be less willing, or unwilling, to protect trade secrets. If a competitor lawfully obtained or independently developed any of our trade secrets, we would have no right to prevent

such competitor from using that technology or information to compete with us, which could harm our competitive position.

Risks Related to Intellectual Property Litigation

We may become involved in lawsuits or other proceedings to protect or enforce our intellectual property, which could be expensive, time-consuming and unsuccessful and have a material adverse effect on the success of our business.

Third parties may infringe our or our licensor's patents or misappropriate or otherwise violate our or our licensor's intellectual property rights. In the future, we or our licensor may initiate legal proceedings to enforce or defend our or our licensor's intellectual property rights, to protect our or our licensor's trade secrets or to determine the validity or scope of intellectual property rights we own or control. Also, third parties may initiate legal proceedings against us or our licensor to challenge the validity or scope of intellectual property rights we own, control or to which we have rights. For example, generic or biosimilar drug manufacturers or other competitors or third parties may challenge the scope, validity or enforceability of our or our licensor's patents, requiring us or our licensor to engage in complex, lengthy and costly litigation or other proceedings. These proceedings can be expensive and time-consuming and many of our or our licensor's adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. Moreover, the outcome following legal assertions of invalidity and unenforceability is unpredictable. Accordingly, despite our or our licensor's efforts, we or our licensor may not be able to prevent third parties from infringing upon or misappropriating intellectual property rights we own, control or have rights to, particularly in countries where the laws may not protect those rights as fully as in the United States. Litigation could result in substantial costs and diversion of management resources, which could harm our business and financial results. In addition, if we or our licensor initiated legal proceedings against a third party to enforce a patent covering a product candidate, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. In an infringement or declaratory judgment proceeding, a court may decide that a patent owned by or licensed to us is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our or our licensor's patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our or our licensor's patents at risk of being invalidated, narrowed, held unenforceable or interpreted in such a manner that would not preclude third parties from entering the market with competing products.

Third-party pre-issuance submission of prior art to the USPTO, or opposition, derivation, revocation, reexamination, *inter partes* review or interference proceedings, or other pre-issuance or post-grant proceedings or other patent office proceedings or litigation in the United States or other jurisdictions provoked by third parties or brought by us or our licensor, may be necessary to determine the inventorship, priority, patentability or validity of inventions with respect to our or our licensor's patents or patent applications. An unfavorable outcome could leave our technology or product candidates without patent protection, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or could require us or our licensor to obtain license rights from the prevailing party in order to be able to manufacture or commercialize our product candidate or any future product candidates without infringing third-party patent rights. Our business could be harmed if the prevailing party does not offer us or our licensor a license on commercially reasonable terms, or at all. Even if we or our licensor obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us or our licensor. In addition, if the breadth or strength of protection provided by our or our licensor's patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or any future product candidates. Even if we successfully defend such litigation or proceeding, we may incur substantial costs and it may distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into collaborations.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, many foreign jurisdictions have rules of discovery that are different than those in the United

States and which may make defending or enforcing our or our licensor's patents extremely difficult. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock.

Third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights or we may initiate legal proceedings against third parties to challenge the validity or scope of intellectual property rights controlled by third parties, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell any product candidates that we may develop and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Third parties may initiate legal proceedings against us or our licensor alleging that we or our licensor infringe their intellectual property rights or we or our licensor may initiate legal proceedings against third parties to challenge the validity or scope of intellectual property rights controlled by third parties, including in oppositions, interferences, revocations, reexaminations, *inter partes* review or derivation proceedings before the USPTO or its counterparts in other jurisdictions. These proceedings can be expensive and time-consuming and many of our or our licensor's adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we or our licensor can.

An unfavorable outcome in any such proceeding could require us or our licensor to cease using the related technology or developing or commercializing our product candidate or any future product candidates, or to attempt to license rights to it from the prevailing party, which may not be available on commercially reasonable terms, or at all.

We could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidate or any future product candidates or force us to cease some of our business operations, which could materially harm our business.

We perform searches of patent and scientific databases in order to identify documents that may be of potential relevance to the freedom-to-operate and/or patentability of our product candidate or any future product candidates. In general, such searches are conducted based on keywords, sequences, inventors/authors and assignees/entities to capture U.S. and European patents and patent applications, PCT publications and scientific journal articles.

The patent landscape around our EFX product candidate is complex, and we may not be aware of all third-party intellectual property rights potentially relating to our product candidate or any future product candidates and technologies. Moreover, it is possible that we are or may become aware of patents or pending patent applications that we think do not relate to our product candidate or any future product candidates or that we believe are invalid or unenforceable, but that may nevertheless be interpreted to encompass our product candidate or any future product candidates and to be valid and enforceable. As to pending third-party applications, we cannot predict with any certainty which claims will issue, if any, or the scope of such issued claims. If any third-party intellectual property claims are asserted against us, even if we believe the claims are without merit, there is no assurance that a court would find in our favor, e.g., on questions of infringement, validity, enforceability or priority. A court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and adversely affect our ability and the ability of our licensor to commercialize any product candidates we may develop, and any other product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If any such third-party patents (including those that may issue from such applications) were successfully asserted against us or our licensor or other commercialization partners and we were unable to successfully challenge the validity or enforceability of any such asserted patents, then we or our licensor and other commercialization partners may be prevented from commercializing our product candidate or any future product candidates, or may be required to pay significant damages, including treble damages and attorneys' fees if we are found to willfully infringe the asserted patents, or obtain a license to such patents, which may not be available 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. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have material adverse effect on our ability to raise additional funds or otherwise have a material adverse effect on our business, results of operations, financial condition and prospects. Any of the foregoing would have a material adverse effect on our business, financial condition and operating results.

We may be subject to claims by third parties asserting that our employees or we have misappropriated a third party's intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees, including our senior management, were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Some of these employees executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. We may be subject to claims that we or these employees have used or disclosed confidential information or intellectual property, including trade secrets or other proprietary information, of any such employee's former employer, or that third parties have an interest in our patents as an inventor or co-inventor. Litigation may be necessary to defend against these claims. 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 or sustain other damages. 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. Such a license may not be available on commercially reasonable terms, or at all. Even if we successfully prosecute or defend against such claims, litigation could result in substantial costs and distract management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to any product candidates we may develop or utilize similar technology but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our current or future collaborators, might not have been the first to make the inventions covered by the issued patents and pending patent applications that we license or may own in the future;
- we, or our current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and

- we may choose not to file a patent application 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.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or the USPTO.

If we or our licensing partner initiate legal proceedings against a third party to enforce a patent covering our product candidate or any future product candidates, the defendant could counterclaim that the patent covering our product candidate, as applicable, is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. These types of mechanisms include *inter partes* review, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). These types of proceedings could result in revocation or amendment to our patents such that they no longer cover our product candidates. The outcome for any particular patent 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 we, our patent counsel and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, or if we are otherwise unable to adequately protect our rights, we would lose at least part, and perhaps all, of the patent protection on our product candidates. A loss of patent protection for our product candidates could have a material adverse impact on our ability to commercialize or license our technology and product candidates and, resultantly, on our business, financial condition, prospects and results of operations.

Likewise, patents directed to our proprietary technologies and our product candidates may expire before or soon after our first product achieves marketing approval in the United States or foreign jurisdictions. Upon the expiration of our current patents, we may lose the right to exclude others from practicing these inventions. The expiration of these patents could also have a similar material adverse effect on our business, financial condition, prospects and results of operations. A number of U.S. patents directed to various aspects of EFX will expire in 2029; we currently anticipate that a composition of matter patent will be eligible for patent term extension to 2034.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidate or any future product candidates.

As is the case with other biotechnology and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involves technological and legal complexity, and obtaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances, weakening the rights of patent owners in certain situations or ruling that certain subject matter is not eligible for patent protection. In addition to increasing uncertainty with regard to our and our licensor's ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by Congress, the federal courts, the USPTO and equivalent bodies in foreign jurisdictions, the laws and regulations governing patents could change in unpredictable ways that would weaken our and our licensor's ability to obtain new patents or to enforce existing patents and patents we and our licensor may obtain in the future.

Patent reform laws, such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, as well as changes in how patent laws are interpreted, could increase the uncertainties and costs surrounding the prosecution of our and our licensor's patent applications and the enforcement or defense of our or our licensor's issued patents, all of which could have a material adverse effect on our business, financial condition and results of operations.

Risks Related to Government Regulation

Risks Related to Obtaining Regulatory Approval

We have limited experience in conducting clinical trials and have never obtained approval for any product candidates, and may be unable to do so successfully.

As a company, other than the completed BALANCED study and our ongoing HARMONY and SYMMETRY studies, we have no experience in designing, conducting or completing clinical trials and have never progressed a product candidate through to regulatory approval. In part because of this lack of experience, our clinical trials may require more time and incur greater costs than we anticipate. We cannot be certain that the planned clinical trials will begin or conclude on time, if at all. Large-scale trials will require significant additional financial and management resources. Any performance failure on the part of such third parties could delay the clinical development of our product candidate or any future product candidates or delay or prevent us from obtaining regulatory approval or commercializing our current or any future product candidates, depriving us of potential product revenue and resulting in additional losses.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. Our inability to obtain regulatory approval for EFX or any future product candidate would substantially harm our business.

The time required to obtain approval from the FDA and comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of nonclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's development and may vary among jurisdictions.

EFX or our future product candidates could fail to receive regulatory approval from the FDA or a comparable foreign regulatory authority for many reasons, including:

- disagreement with the design or implementation of our clinical trials;
- failure to demonstrate that a product candidate is safe and effective for its proposed indication;
- failure of clinical trials to meet the level of statistical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- disagreement with our interpretation of data from nonclinical studies or clinical trials;
- the insufficiency of data collected from clinical trials of EFX or any future product candidates to obtain regulatory approval;
- failure to obtain approval of the manufacturing processes or facilities of third-party manufacturers with whom we contract for clinical and commercial supplies; or
- changes in the approval policies or regulations that render our nonclinical and clinical data insufficient for approval.

The FDA or a comparable foreign regulatory authority may require more information, including additional nonclinical or clinical data to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program for other reasons. If we were to obtain approval, regulatory authorities may approve EFX or any future product candidates for fewer or more limited indications than we request, may require labeling or a Risk Evaluation Mitigation Strategy, or REMS, that includes significant use or distribution restrictions or safety warnings, precautions, or contraindications, 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.

During the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications.

Additional time may be required to obtain regulatory approval for our product candidates because they are combination products.

EFX is being developed, and future product candidates may be developed, as combination products that require coordination within the FDA and similar foreign regulatory agencies for review of their device and drug/biologic components. Medical products containing a combination of new drugs, biological products or medical devices may be regulated as "combination products" in the United States and Europe. A combination product generally is defined as a product comprised of components from two or more regulatory categories (e.g., drug/device, device/biologic, drug/biologic). Each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a new drug, biologic or device. In order to facilitate premarket review of combination products, the FDA designates one of its centers to have primary jurisdiction for the pre-market review and regulation of the overall product based upon a determination by the FDA of the primary mode of action of the combination product. Where approval of the drug or biologic and device is sought under a single application, there could be delays in the approval process due to the increased complexity of the review process and the lack of a well-established review process and criteria. The EMA has a parallel review process in place for combination products, the potential effects of which in terms of approval and timing could independently affect our ability to market our combination products in Europe.

While we intend to seek designations for our product candidates with the FDA and comparable other regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

In addition, in October 2021, the FDA granted Fast Track designation for EFX for the treatment of NASH, and we may seek Fast Track Designation for some of our future product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, as we have for EFX for the treatment of NASH, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA

approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

Biologics designated as breakthrough therapies or granted Fast Track designation by the FDA may also be eligible for other expedited approval programs, including accelerated approval. A product candidate may be eligible for accelerated approval if it treats a serious or life-threatening condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. As a condition of accelerated approval, the FDA may require that a sponsor of a product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. These confirmatory trials must be completed with due diligence. Under FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of approval for a product granted accelerated approval. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. In addition, FDORA gives the FDA increased authority to withdraw accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. The FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. Accelerated approval may also be withdrawn if, among other things, a confirmatory trial required to verify the predicted clinical benefit of the product fails to verify such benefit or if such trial is not conducted with due diligence. In addition, the FDA generally requires, unless otherwise informed by the agency, pre-approval of promotional materials for products receiving accelerated approval, which could adversely impact the timing of the commercial launch of the product. Thus, even if we seek to utilize the accelerated approval pathway, we may not be able to obtain accelerated approval and, even if we do, we may not experience a faster development, regulatory review or approval process for that product. In addition, receiving accelerated approval does not assure that the product's accelerated approval will eventually be converted to a traditional approval.

We may seek priority review designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

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

Our failure to obtain regulatory approval in international jurisdictions would prevent us from marketing EFX or any future product candidates outside the United States.

We intend to market any approved products in the United States, the EU, Japan and other foreign jurisdictions. Even if our products are approved for marketing in the United States, in order to market and sell our products in other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying 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, we must secure product reimbursement approvals before regulatory authorities will approve the product for sale in that country. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country. For example, even if EFX is approved in the United States, the EMA may require more information, including additional nonclinical or clinical data to support approval, which may delay or prevent approval and our

commercialization plans in the EU. Moreover, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others.

Also, regulatory approval for our product candidate or any future product candidates may be withdrawn if we fail to comply with regulatory requirements, if problems occur after the product candidate reaches the market or for other reasons. If we fail to comply with the regulatory requirements in international markets and fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidate or any future product candidates will be harmed and our business will be adversely affected. We may not obtain foreign regulatory approvals on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions. 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. If we fail to obtain approval of our product candidate or any future product candidates by regulatory authorities in another country, we will be unable to commercialize our product in that country, and the commercial prospects of that product candidate and our business prospects could decline.

Risks Related to Ongoing Regulatory Obligations

Even if we are able to obtain regulatory approvals for our product candidate or any future product candidates, if they exhibit harmful side effects after approval, our regulatory approvals could be revoked or otherwise negatively impacted, and we could be subject to costly and damaging product liability claims.

Clinical trials are conducted in representative samples of the potential patient population which may have significant variability. Even if we receive regulatory approval for EFX or any of our future product candidates, we will have tested them in only a small number of patients during our clinical trials. Clinical trials are by design based on a limited number of subjects and of limited duration for exposure to the product used to determine whether, on a potentially statistically significant basis, the planned safety and efficacy of any product candidate can be achieved. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered, and it may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration, may a more complete safety profile be identified. Further, even larger clinical trials may not identify rare serious adverse effects or the duration of such studies may not be sufficient to identify when those events may occur. If our applications for marketing are approved and more patients begin to use our product, new risks and side effects associated with our products may be discovered. There have been other products that have been approved by the regulatory authorities but for which safety concerns have been uncovered following approval. Such safety concerns have led to labelling changes or withdrawal of products from the market, and any of our product candidates may be subject to similar risks. Additionally, we may be required to conduct additional nonclinical and clinical trials, require additional warnings on the label of our product candidate, reformulate our product or make changes, create a medication guide outlining the risks of such side effects for distribution to patients and obtain new approvals for our and our suppliers' manufacturing facilities for EFX and any future product candidates. We might have to withdraw or recall our products from the marketplace. We may also experience a significant drop in the potential sales of our product if and when regulatory approvals for such product are obtained, experience harm to our reputation in the marketplace or become subject to lawsuits, including class actions. Any of these results could decrease or prevent any sales of our approved product or substantially increase the costs and expenses of commercializing and marketing our product.

Even if our current product candidate or any future product candidates receive regulatory approval, they will remain subject to extensive regulatory scrutiny and may still face future development and regulatory difficulties.

Even if we obtained regulatory approval for a product candidate, regulatory authorities may still impose significant restrictions on our product candidates, including their indicated uses or marketing, or impose ongoing requirements for potentially costly post-approval studies. For example, if EFX is approved by the FDA based on a surrogate endpoint pursuant to accelerated approval regulations (also referred to as Subpart E regulations), we will be required to conduct additional confirmatory clinical trials demonstrating the clinical benefit on the ultimate outcome of NASH. Further, even if we obtained regulatory approval for a product candidate, it would be subject to ongoing requirements by the FDA and comparable foreign regulatory authorities governing the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

The FDA and comparable foreign regulatory authorities will continue to closely monitor the safety profile of any product even after approval. If the FDA or comparable foreign regulatory authorities become aware of new safety information after approval of our product candidate or any future product candidates, they may require labeling changes or establishment of a risk evaluation and mitigation strategy or similar strategy, impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance.

In addition, manufacturers of our products, if approved, and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP and applicable QSRs, regulations and standards. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we, EFX, or any future product candidates or the manufacturing facilities for EFX, the delivery device used for EFX, or any future product candidates fail to comply with applicable regulatory requirements, or undesirable side effects caused by such products are identified, a regulatory agency may:

- issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about such product;
- mandate modifications to instructions for use;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require that we conduct post-marketing studies;
- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend marketing of, withdraw regulatory approval of or recall such product;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products or require us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product and generate revenue.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by the FDA, the Department of Justice, the Department of Health and Human Services' Office of Inspector General, state attorneys general, members of Congress and the public. Violations, including promotion of our products for unapproved (or off-label) uses, are subject to enforcement letters, inquiries and investigations, and civil and criminal sanctions by the government. Additionally, comparable foreign regulatory authorities will heavily scrutinize advertising and promotion of any product candidate that obtains approval outside of the United States.

In the United States, engaging in the impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. Since 2004, these federal False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements regarding certain sales practices promoting off-label drug uses involving fines in excess of $1 billion. This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations and be excluded from Medicare, Medicaid and other federal and state healthcare programs. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we do

not successfully defend against such actions, those actions may have a material adverse effect on our business, financial condition and results of operations.

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

Risks Related to Healthcare Regulation

The advancement of healthcare reform may negatively impact our ability to profitably sell our product candidate or any future product candidates, if approved.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidate or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements.

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

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction, which triggered the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year through 2031 unless Congress takes additional action. Due to the Statutory Pay-As-You-Go Act of 2010, estimated budget deficit increases resulting from the American Rescue Plan Act of 2021, and subsequent legislation, Medicare payments to providers will be further reduced starting in 2025 absent further legislation. In January 2013, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On April 13, 2017, CMS published a final rule that gives states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. In May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Additionally, on December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repealed the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future.

There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs.

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

On November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Additionally, on November 30, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. This deadline was pushed back to January 1, 2027 by the Bipartisan Safer Communities Act. The Inflation Reduction Act of 2022 further delayed implementation of this rule to January 1, 2032.

Further, on December 31, 2020, CMS published a new rule, effective January 1, 2023, requiring manufacturers to ensure the full value of co-pay assistance is passed on to the patient or these dollars will count toward the Average Manufacturer Price and Best Price calculation of the drug. On May 17, 2022, the U.S. District Court for the District of Columbia granted the Pharmaceutical Research and Manufacturers of America's (PhRMA) motion for summary judgment invalidating the accumulator adjustment rule.

In August 2022, the Inflation Reduction Act of 2022 (the "IRA") was signed into law. The IRA includes several provisions that will impact our business to varying degrees, including provisions that create a $2,000 out-of-pocket cap for Medicare Part D beneficiaries, impose new manufacturer financial liability on all drugs in Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D pricing for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for drug prices that increase faster than inflation, and delay the rebate rule that would require pass through of pharmacy benefit manager rebates to beneficiaries. The effect of IRA on our business and the healthcare industry in general is not yet known.

We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our approved products;
- our ability to generate revenue and achieve or maintain profitability;

- the level of taxes that we are required to pay; and
- the availability of capital.

Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors, which may adversely affect our future profitability. Although a number of these, and other proposed measures may require additional authorization to become effective, and the Biden administration may reverse or otherwise change these measures, Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly passed legislation and implemented 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.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private third-party payors.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which, if violated, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens 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 product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research, and if approved, market, sell and distribute our products. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits persons from, among other things, knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, the referral of an individual for the furnishing or arranging for the furnishing, or the purchase, lease or order, or arranging for or recommending purchase, lease or order, of any good or service for which payment may be made under a federal healthcare program, such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which can be enforced through civil whistleblower or *qui tam* actions, prohibit individuals or entities from, among other things knowingly presenting, or causing to be presented, to the federal government or a government contractor, grantee, or other recipient of federal funds, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; knowingly making, using or causing to be made or used, a false statement or record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or knowingly concealing or knowingly and improperly avoiding or

decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal liability for knowingly and willfully executing a scheme to defraud any healthcare benefit program, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense or knowingly and willfully making false statements relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their implementing regulations, including the Final Omnibus Rule published in January 2013, imposes obligations on certain healthcare providers, health plans and healthcare clearinghouses, known as covered entities, as well as their business associates, which are individuals and entities that perform certain services involving the creation, maintenance, receipt, use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;
- federal price reporting laws, which require manufacturers to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and/or discounts on approved products;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- the federal Open Payments program, created under Section 6002 of the Affordable Care Act and its implementing regulations, requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to CMS information related to "payments or other transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians (as defined above) and their immediate family members. As of January 1, 2022, these reporting obligations have now extended to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners; and
- analogous state, local, and foreign 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 payors, including private insurers; state and foreign 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 or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug prices; state and local laws that require the registration of pharmaceutical sales representatives; several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the EU General Data Protection Regulation, which became effective May 2018 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; and state and foreign laws that govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties 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 interpreting 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, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, that person or entity may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business.

We and any potential collaborators may be subject to federal, state, and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act and California Consumer Privacy Act of 2018 ("CCPA")), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. The state of California, for example, recently adopted the CCPA, which went into effect beginning in January 2020. The CCPA has been characterized as the first "GDPR-like" privacy statute to be enacted in the United States because it mirrors a number of the key provisions of the EU General Data Protection Regulation, or GDPR (discussed below in the European Data Collection subsection). The CCPA establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact some of our business activities.

Further, the California Privacy Rights Act, or CPRA, was passed by California voters on November 3, 2020 and entered into force on January 1, 2023. The CPRA creates additional obligations with respect to processing and storing personal information. Additionally, some observers have noted that the CCPA and CPRA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business. Already, in the United States, we have witnessed significant developments at the state level. For example, on March 2, 2021, Virginia enacted the Consumer Data Protection Act (the "CDPA") and, on July 8, 2021, Colorado's governor signed the Colorado Privacy Act ("CPA"), into law. The CDPA became effective on January 1, 2023 and the CPA will become effective July 1, 2023. While the CDPA and CPA incorporate many similar concepts of the CCPA and CPRA, there are also several key differences in the scope, application, and enforcement of the law that will change the operational practices of regulated businesses. The new laws will, among other things, impact how regulated businesses collect and process personal sensitive data, conduct data protection assessments, transfer personal data to affiliates, and respond to consumer rights requests.

A number of other states have proposed new privacy laws, some of which are similar to the above discussed recently passed laws. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs and/or changes in business practices and policies. The existence of comprehensive privacy laws in different states in the country would make our compliance obligations more complex and costly and may increase the likelihood that we may be subject to enforcement actions or otherwise incur liability for noncompliance.

Compliance with U.S. and international data protection laws and regulations, including the EU GDPR/UK GDPR and other EU and UK data protection laws could require us to take on more onerous obligations in our contracts,

restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects, employees and other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

In the event we decide to conduct clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area ("EEA"), including personal health data, is subject to the EU General Data Protection Regulation ("EU GDPR"), and similarly, processing of personal data regarding individuals in the UK is subject to the UK General Data Protection Regulation and the UK Data Protection Act 2018 ("UK GDPR" and together with the EU GDPR, "GDPR"). The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EEA/UK, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million (£17.5 million under UK GDPR) or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR includes restrictions on cross-border data transfers of personal data to countries outside the EEA/UK that are not considered by the European Commission and UK government as providing "adequate" protection to personal data ("third countries"), including the United States. The GDPR may increase our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities.

To enable the transfer of personal data outside of the EEA or the UK, adequate safeguards (for example, the European Commission approved Standard Contractual Clauses ("SCCs")) must be implemented in compliance with European and UK data protection laws. In addition, transfers made pursuant to the SCCs (and other similar appropriate transfer safeguards) need to be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular regarding applicable surveillance laws and relevant rights of individuals with respect to the transferred personal data, to ensure an "essentially equivalent" level of protection to that guaranteed in the EEA in the jurisdiction where the data imported is based ("Transfer Impact Assessment"). On June 4, 2021, the EC issued new forms of standard contractual clauses for data transfers from controllers or processors in the EU/EEA (or otherwise subject to the GDPR) to controllers or processors established outside the EU/EEA. The new standard contractual clauses replace the standard contractual clauses that were adopted previously under the EU Data Protection Directive. The UK is not subject to the EC's new standard contractual clauses but has published its own transfer mechanism, the International Data Transfer Agreement and International Data Transfer Addendum ("IDTA"), a which will enable transfers from the UK, and has also implemented a similar Transfer Impact Assessment requirement. We will be required to implement these new safeguards and carry out Transfer Impact Assessments when conducting restricted data transfers under the GDPR and doing so will require significant effort and cost, and may result in us needing to make strategic considerations around where EEA or UK personal data is stored and transferred, and which service providers we can utilize for the processing of EEA/UK personal data.

Although the UK is regarded as a third country under the EU GDPR, the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR ("Adequacy Decision") and, therefore, transfers of personal data originating in the EEA to the UK remain unrestricted. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing. The UK Government has also now introduced a Data Protection and Digital Information Bill ("UK Bill") into the UK legislative process. The aim of the UK Bill is to reform the UK's data protection regime following Brexit. If passed, the final version of the UK Bill may

have the effect of further altering the similarities between the UK and EEA data protection regime and threaten the UK Adequacy Decision from the EU Commission. This may lead to additional compliance costs and could increase our overall risk. The respective provisions and enforcement of the EU GDPR and UK GDPR may further diverge in the future and create additional regulatory challenges and uncertainties.

Compliance with the above and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenue, if any.

In some countries, particularly the countries of the EU, 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 drug. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our drug candidate to other available procedures. If reimbursement of our drugs is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Healthcare insurance coverage and reimbursement may be limited or unavailable for our product candidate, if approved, which could make it difficult for us to sell our product candidate or other therapies profitably.

The success of our product candidate, if approved, depends on the availability of coverage and adequate reimbursement from third-party payors including governmental healthcare programs, such as Medicare and Medicaid, commercial payors, and health maintenance organizations. We cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Coverage and adequate reimbursement from third-party payors are critical to new product acceptance.

Third-party payors decide which drugs and treatments they will cover and the amount of reimbursement. 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, 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 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. There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by CMS, an agency within HHS, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private third-party payors tend to follow Medicare coverage and reimbursement limitations to a substantial degree, but also have their own methods and approval process apart from Medicare determinations. Even if we obtain coverage for a given product, the resulting reimbursement payment rates

might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high.

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.

Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement.

In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs.

Our activities in the United States subject us to various laws relating to foreign investment and the export of certain technologies, and our failure to comply with these laws or adequately monitor the compliance of our suppliers and others we do business with could subject us to substantial fines, penalties and even injunctions, the imposition of which on us could have a material adverse effect on the success of our business.

Because we have substantial operations in the United States, we are subject to U.S. laws that regulate foreign investments in U.S. businesses and access by foreign persons to technology developed and produced in the United States. These laws include Section 721 of the Defense Production Act of 1950, as amended by the Foreign Investment Risk Review Modernization Act of 2018, and the regulations at 31 C.F.R. Parts 800 and 801, as amended, administered by the Committee on Foreign Investment in the United States; and the Export Control Reform Act of 2018, which is being implemented in part through Commerce Department rulemakings to impose new export control restrictions on "emerging and foundational technologies" yet to be fully identified. Application of these laws, including as they are implemented through regulations being developed, may negatively impact our business in various ways, including by restricting our access to capital and markets; limiting the collaborations we may pursue; regulating the export our products, services, and technology from the United States and abroad; increasing our costs and the time necessary to obtain required authorizations and to ensure compliance; and threatening monetary fines and other penalties if we do not.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties to sell our products sell our products outside the United States, to conduct clinical trials, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

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 or existing product candidates 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, the ability to hire and retain key personnel and accept payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of 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 drug candidates to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. 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, in our operations as a public company, 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.

Risks Related to Our Financial Condition and Need for Additional Capital

We have incurred significant losses since our inception and we expect to incur losses for the foreseeable future.

We have no products approved for commercial sale and have not generated any revenue to date, and we continue to incur significant research and development and other expenses related to our ongoing operations. As a result, we are not profitable and have incurred significant losses in each period since our inception in January 2017. For the years ended December 31, 2022 and 2021, we reported net losses of $112.0 million and $100.8 million, respectively. As of December 31, 2022, we had an accumulated deficit of $422.3 million. We expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for, our product candidate. We anticipate that our expenses will increase substantially if, and as, we:

- conduct larger scale clinical trials for our product candidate, EFX, and any future product candidates;
- discover and develop new product candidates, and conduct nonclinical studies and clinical trials;
- incur setbacks or delays to the initiation or completion of preclinical and non-clinical studies, product development and/or clinical trials due to the COVID-19 pandemic;
- incur any disruption or delays to the supply of our product candidate due to the COVID-19 pandemic;
- manufacture, or have manufactured, clinical and commercial supplies of our product candidates;
- seek regulatory approvals for EFX or any future product candidates;
- commercialize EFX or any future product candidates, if approved;
- attempt to transition from a company with a development focus to a company capable of supporting commercial activities, including establishing sales, marketing and distribution infrastructure;
- hire additional clinical, scientific, and management personnel;
- add operational, financial, and management information systems and personnel;
- identify additional compounds or product candidates and acquire rights from third parties to those compounds or product candidates through licenses; and
- incur additional costs associated with operating as a public company.

Even if we succeed in commercializing EFX or any future product candidates, we may continue to incur substantial research and development and other expenditures to develop and market additional product candidates. 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. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital.

We currently have a limited operating history, have not generated any revenue to date, and may never become profitable.

We are a clinical-stage biotechnology company with a limited operating history. Our operations to date have been limited to organizing and staffing our company, acquiring, developing and securing our technology and product candidate, EFX, and conducting nonclinical studies and clinical trials of EFX. We have not yet demonstrated our ability to complete late-stage clinical trials, obtain regulatory approval, formulate and manufacture a commercial-scale product, or conduct sales and marketing activities necessary for successful product commercialization. Investment in biotechnology product development is highly speculative because it entails substantial upfront expenditures in clinical research organizations and contract manufacturing organizations and significant risk that any potential product candidate will fail to demonstrate adequate effect or an acceptable safety profile, gain regulatory approval and become commercially viable. Consequently, any predictions you may make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Though EFX is currently in Phase 2 clinical development, we do not expect to receive revenue from EFX for a number of years, if ever. To date, we have not generated any revenue and we will not be able to generate product revenue unless and until EFX, or any future product candidate, successfully completes clinical trials, receives regulatory approval, and is commercialized. We may seek to obtain revenue from collaboration or licensing agreements with third parties. Our ability to generate future product revenue from EFX or any future product candidates also depends on a number of additional factors, including our, or our current and future contractors' and collaborators', ability to:

- successfully complete nonclinical studies and clinical trials for EFX and any future product candidates;
- seek and obtain marketing approvals for any product candidates that complete clinical development;
- establish and maintain supply and manufacturing relationships with third parties, and ensure adequate and legally compliant manufacturing of bulk drug substances and drug products to maintain that supply;
- launch and commercialize any product candidates for which we obtain marketing approval, and, if launched independently, successfully establish a sales, marketing and distribution infrastructure;
- demonstrate the necessary safety data post-approval to ensure continued regulatory approval;
- obtain coverage and adequate product reimbursement from third-party payors, including government payors;
- achieve market acceptance for any approved products;
- address any competing technological and market developments;
- maintain our rights under our existing license agreement with Amgen and any similar agreements we may enter into in the future;
- negotiate favorable terms in any collaboration, licensing or other arrangements into which we may enter in the future and performing our obligations in such collaborations;
- establish, maintain, protect and enforce our intellectual property rights; and
- attract, hire and retain qualified personnel.

In addition, because of the numerous risks and uncertainties associated with biotechnology product development, including that our product candidate may not advance through development or achieve the endpoints of applicable clinical trials, we are unable to predict the timing or amount of increased expenses, or if or when we will achieve or maintain profitability. In addition, our expenses could increase beyond expectations if we decide, or are required by the FDA or foreign regulatory authorities, to perform nonclinical studies or clinical trials in addition to those that we currently anticipate. Even if we complete the development and regulatory processes described above, we anticipate incurring significant costs associated with launching and commercializing any approved product.

If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

We will require additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. As a result, we may not complete the development and commercialization of our product candidate or develop any future product candidates.

As a research and development company, our operations have consumed substantial amounts of cash since inception. We expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance EFX into later-stage clinical development.

As of December 31, 2022, we had $351.4 million of cash, cash equivalents and short-term marketable securities. We raised gross proceeds of $105.8 million from our initial public offering in June 2019 and $216.4 million from our follow-on public offering in July 2020. We also raised gross proceeds of $25.0 million from Pfizer through a registered direct common stock offering and $10.0 million from Hercules under a term loan in June 2022. In addition, we raised gross proceeds of $230.0 million from a follow-on public offering in September 2022. Any forecast of the period of time through which our financial resources will adequately support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors, including the factors discussed elsewhere in this "Risk Factors" section. The assumptions underlying any estimate may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both short and long-term, will depend on many factors, including, but not limited to:

- the initiation, progress, timing, costs and results of nonclinical studies and clinical trials for our product candidate or any future product candidates we may develop, including on account of any setbacks or delays due to the COVID-19 pandemic;
- the cost and timing of manufacturing our product candidate for use in clinical trials or, if approved by the FDA, for commercial use, including on account of any disruption or delays to the supply of our product candidate due to the COVID-19 pandemic;
- our ability to maintain our license to EFX from Amgen;
- the outcome, timing and cost of seeking and obtaining regulatory approvals from the FDA and comparable foreign regulatory authorities, including the potential for such authorities to require that we perform more nonclinical studies or clinical trials than those that we currently expect or change their requirements on studies that had previously been agreed to;
- the cost to establish, maintain, expand, enforce and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with licensing, preparing, filing, prosecuting, defending and enforcing any patents or other intellectual property rights;
- the effect of competing technological and market developments;
- market acceptance of any approved product candidates, including product pricing, as well as product coverage and the adequacy of reimbursement by third-party payors;
- the cost of acquiring, licensing or investing in additional businesses, products, product candidates and technologies;
- the cost and timing of selecting, auditing and potentially validating a manufacturing site for commercial scale manufacturing;
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval and that we determine to commercialize; and
- our need to implement additional internal systems and infrastructure, including financial and reporting systems.

We do not have any committed external source of funds or other support for our development efforts and we cannot be certain that additional funding will be available on acceptable terms, or at all. Until we can generate sufficient revenue to finance our cash requirements, which we may never do, we expect to finance our future cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements, and other marketing or distribution arrangements. If we raise additional funds through public or private equity offerings, the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. Further, to the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, your ownership interest will be diluted. If we raise additional capital through debt financing, we could be subject to fixed payment obligations and may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring

dividends. If we raise additional capital through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. We also could be required to seek collaborators for one or more of our current or any future product candidates at an earlier stage than otherwise would be desirable or relinquish our rights to product candidates or technologies that we otherwise would seek to develop or commercialize ourselves. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our products or product candidates or one or more of our other research and development initiatives. 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.

Risks Related to Our Indebtedness

Our operating activities may be restricted as a result of covenants related to our term loan obligation, which we may be required to repay in an event of default, which could have a materially adverse effect on our business.

On June 15, 2022, we entered into a Loan and Security Agreement ("Loan Agreement") with Hercules Capital, Inc., ("Hercules") for an aggregate principal amount of up to $100.0 million. Until we have repaid such indebtedness, the Loan Agreement subjects us to various customary covenants, including requirements as to financial reporting and insurance, and restrictions on our ability to dispose of our business or property, to change our line of business, to liquidate or dissolve, to merge or consolidate with any other entity or to acquire all or substantially all the capital stock or property of another entity, to incur additional indebtedness, to incur liens on our property, to pay any dividends or other distributions on capital stock other than dividends payable solely in capital stock, to redeem capital stock, to enter into licensing agreements, to engage in transactions with affiliates, or to encumber our intellectual property. Additionally, there is a financial covenant requiring us to maintain a minimum cash balance in relation to the outstanding principal balance of the Term Loan. Our business may be adversely affected by these restrictions on our ability to operate our business.

Additionally, we may be required to repay the outstanding indebtedness under the Term Loan if an event of default occurs under the Loan Agreement. Under the Loan Agreement, an event of default will occur if, among other things: we fail to make payments under the Loan Agreement; we breach any of our covenants under the Loan Agreement, subject to specified cure periods with respect to certain breaches; the Lender determines that a material adverse change has occurred; we or our assets become subject to certain legal proceedings, such as bankruptcy proceedings; we are unable to pay our debts as they become due; or we default on contracts with third parties which would permit the holder of indebtedness to accelerate the maturity of such indebtedness or that could have a material adverse change on us. As a result of the occurrence of an event of default, Hercules could accelerate all of the amounts due. In the event of an acceleration of amounts due under the Term Loan, we may not have enough available cash or be able to raise additional funds through equity or debt financings to repay such indebtedness at the time any such event of default occurs. In this case, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant to others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Our business, financial condition and results of operations could be materially adversely affected as a result of any of these events.

Our level of indebtedness and debt service obligations could adversely affect our financial condition and may make it more difficult for us to fund our operations.

The Term Loan with Hercules provides up to $100.0 million of debt financing and has interest-only payments through July 1, 2024, which may be extended based on achievement of certain milestones. Thereafter, we are obligated to make payments that will include equal installments of principal and interest through the maturity date of January 1, 2027.

This indebtedness may create additional financing risk for us, particularly if our business or prevailing financial market conditions are not conducive to paying off or refinancing our outstanding debt obligations at maturity. This indebtedness could also have important negative consequences, including the fact that:

- we will need to repay our indebtedness by making payments of interest and principal, which will reduce the amount of money available to finance our operations, our research and development efforts and other general corporate activities; and
- our failure to comply with the restrictive covenants in the Term Loan could result in an event of default that, if not cured or waived, would accelerate our obligation to repay this indebtedness, and Hercules could seek to enforce our security interest in the assets securing such indebtedness.

Risks Related to Commercialization and Market Acceptance

Risks Related to Commercialization

Even if we commercialize EFX or any future product candidates, if approved, these products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could harm our business.

The regulations that govern marketing approvals, pricing 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 or limit our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenue we generate from the sale of the product in that particular country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidate or any future product candidates obtain marketing approval.

Our ability to commercialize any products 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 third-party payors such as government health administration authorities, private health insurers and other organizations. Third-party payors determine which medications they will cover and establish reimbursement levels. Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval, if any. If coverage and 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 marketing approval is obtained, if any.

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 comparable foreign regulatory authorities. 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. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may only be temporary. 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. Our inability to promptly obtain coverage and profitable reimbursement rates third-party 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.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidate or any future product candidates in human clinical trials and will face an even greater risk if we commercialize any resulting products. Product liability claims may be brought against us by subjects enrolled in our clinical trials, patients, their family members, healthcare providers or others using, administering or selling our products. If we cannot successfully defend ourselves against claims that our product candidate or any future product candidates or products that we may develop caused injuries, we could 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 trial sites or entire trial programs;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial subjects or patients;
- loss of revenue;
- diversion of management and scientific resources from our business operations;
- the inability to commercialize any products that we may develop; and
- a decline in our stock price.

Our clinical trial liability insurance coverage may not adequately cover all liabilities that we may incur. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. Our inability to obtain product liability insurance at an acceptable cost or to otherwise protect against potential product liability claims could prevent or delay the commercialization of any products or product candidates that we develop. We intend to expand our insurance coverage for products to include the sale of commercial products if we obtain marketing approval for our product candidate or any future product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing. Large judgments have been awarded in lawsuits based on drugs that had unanticipated side effects. If we are sued for any injury caused by our products, product candidates or processes, our liability could exceed our product liability insurance coverage and our total assets. Claims against us, regardless of their merit or potential outcome, may also generate negative publicity or hurt our ability to obtain physician adoption of our product or expand our business.

Risks Related to Market Acceptance

If, in the future, we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market any product candidates we may develop, we may not be successful in commercializing those product candidates if and when they are approved.

We do not currently have an infrastructure for the sales, marketing, and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial, and other non-technical capabilities, or make arrangements with third parties to perform these services. There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force or reimbursement specialists 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 and other commercialization capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our commercialization personnel.

If we enter into arrangements with third parties to perform sales, marketing, commercial support, and distribution services, our product revenue or the profitability of product revenue may be lower than if we were to market and sell any products we may develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to commercialize our product candidates or may be unable to do so on terms that are favorable to us. We may 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 and they could expose our company to regulatory enforcement and legal risk in the execution of their sales and commercialization activities. If we do not establish commercialization capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates if approved.

If we are unable to establish adequate sales, marketing, and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition, and prospects will be materially adversely affected.

Our product candidate or any future product candidates may not achieve adequate market acceptance among physicians, patients, third-party payors and others in the medical community necessary for commercial success.

Even if our product candidate or any future product candidates receive regulatory approval, they may not gain adequate market acceptance among physicians, patients, third-party payors, pharmaceutical companies and others in the medical community. Demonstrating the safety and efficacy of our product candidate or any future product candidates and obtaining regulatory approvals will not guarantee future revenue. Our commercial success also depends on coverage and adequate reimbursement of our product candidate or any future product candidates by third-party payors, including government payors and private insurers, which may be difficult or time-consuming to obtain, may be limited in scope and may not be obtained in all jurisdictions in which we may seek to market our products. Third-party payors closely examine medical products to determine whether they should be covered by reimbursement and, if so, the level of reimbursement that will apply. We cannot be certain that third-party payors will sufficiently reimburse sales of our product or enable us to sell our product at a profitable price. Similar concerns could also limit the reimbursement amounts that health insurers or government agencies in other countries are prepared to pay for our products. In many regions, including Europe, Japan and Canada, where we may market our products, the pricing of prescription drugs is controlled by the government or regulatory agencies. Regulatory agencies in these countries could determine that the pricing for our products should be based on prices of other commercially available drugs for the same disease, rather than allowing us to market our products at a premium as new drugs. The degree of market acceptance of any of our approved product candidates will depend on a number of factors, including:

- the efficacy and safety profile of the product candidate as demonstrated in clinical trials;
- the timing of market introduction of the product candidate as well as competitive products;
- any impact to market health as a result of COVID-19;
- the clinical indications for which the product candidate is approved;
- acceptance of the product candidate as a safe and effective treatment by clinics and patients;
- the potential and perceived advantages of the product candidate over alternative treatments, including any similar generic treatments;
- the cost of treatment in relation to alternative treatments;
- the availability of coverage and adequate reimbursement and pricing by third-party payors;
- the relative convenience and ease of administration;
- the frequency and severity of adverse events;
- the effectiveness of sales and marketing efforts; and
- unfavorable publicity relating to our product candidate or any future product candidates.

Sales of medical products also depend on the willingness of physicians to prescribe the treatment, which is likely to be based on a determination by these physicians that the products are safe, therapeutically effective and cost effective. In addition, the inclusion or exclusion of products from treatment guidelines established by various physician groups and the viewpoints of influential physicians can affect the willingness of other physicians to prescribe the treatment. We cannot predict whether physicians, physicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our product is safe, therapeutically effective and cost effective as compared with competing treatments. If any product candidate is approved but does not achieve an adequate level of acceptance by such parties, we may not generate or derive sufficient revenue from that product candidate and may not become or remain profitable.

Risks Related to Our Operations

We incur significant costs and expend significant time and effort, as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

We incur significant legal, accounting and other expenses, and expend significant time and effort by management and other personnel, to comply with the rules applicable to us as a public company. We are subject to the reporting requirements of Nasdaq and of the Securities Exchange Act of 1934, as amended, which require, among other things, that we file with the Securities and Exchange Commission (SEC), annual, quarterly, and current reports with respect to our business and financial condition and that we establish and maintain effective disclosure controls, procedures and corporate governance practices. We must also comply with the Sarbanes-Oxley Act of 2002 (the "Sarbanes-Oxley Act"), and specifically Section 404 of the Sarbanes-Oxley Act, which requires that we establish and maintain effective internal controls over financial reporting. In order to maintain compliance with the SEC's rules that implement Section 404 of the Sarbanes-Oxley Act, we are required to make a formal assessment of the effectiveness of our internal control over financial reporting, to certify financial and other information in our quarterly and annual reports and to provide an annual management report on the effectiveness of our internal control over financial reporting, which includes the disclosure of any material weaknesses and associated remediation activities. When we are no longer a smaller reporting company, we will incur additional significant costs to meet the requirement to provide an attestation report on our internal control over financial reporting from our independent registered public accounting firm. We will need to continue to dedicate significant internal resources and outside consultants in order to complete management's annual assessment and to prepare for when we are no longer a smaller reporting company. Despite these efforts, there is no guarantee that we will be able to conclude that our internal controls over financial reporting remain effective.

Further, in July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act (the Dodd-Frank Act) was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas, such as "say on pay" and proxy access. Stockholder activism, the current political environment, and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

We expect the rules and regulations applicable to public companies, and the additional compliance requirements that we will be subject to when we are no longer a smaller reporting company, to substantially increase our legal and financial compliance costs and to make some activities more time-consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition, and results of operations. The increased costs will decrease our net income or increase our net loss and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain key financial or management personnel.

If we fail to maintain an effective system of internal controls over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could harm our business and have a negative effect on the trading price of our stock.

If material weaknesses or significant deficiencies in our internal control over financial reporting are identified in the future, we may not detect or remediate errors on a timely basis and our consolidated financial statements may be materially misstated. We, or our independent registered public accounting firm, may not be able to conclude on an ongoing basis that we have effective internal control over financial reporting, which could harm our operating results, cause investors to lose confidence in our reported financial information and cause the trading price of our stock to fall. In addition, any failure to report our financial results on an accurate and timely basis could result in sanctions, lawsuits, delisting of our shares from NASDAQ or other adverse consequences that would materially harm our business.

Our business and operations would suffer in the event of computer system failures, cyber-attacks or deficiencies in our or related parties' cyber security.

Given our limited operating history, we are still in the process of implementing our internal security measures. Our internal computer systems and those of current and future third parties on which we rely may fail and are vulnerable to damage from computer viruses and unauthorized access. Geopolitical instability, including Russia's invasion of Ukraine may increase cyber-attacks. Additionally, cyberattacks could include industrial espionage, wire fraud and other forms of cyber fraud, the deployment of harmful malware, including ransomware, denial-of-service, social engineering fraud or other means to threaten data security, confidentiality, integrity and availability. Although we devote resources to protect our information systems, we realize that cyberattacks are a threat, and there can be no assurance that our efforts will prevent information security breaches that would result in business, legal, financial, or reputational harm to us, or would have a material adverse effect on our results of operations and financial condition. Our information technology and other internal infrastructure systems, including corporate firewalls, servers, leased lines and connection to the Internet, face the risk of systemic failure that could disrupt our operations. A successful cyberattack could result in the theft or destruction of intellectual property, data, or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cyberattacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. 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. While we have not, to our knowledge, experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in the following, which could be material:

- delays in our regulatory approval efforts;
- remediation costs, such as liability for stolen assets or information, repairs of system damage, and incentives to business partners in an effort to maintain relationships after an attack;
- investigation costs, including costs associated with potential notification of the attack to data subjects, regulators or others and costs to engage third party forensic investigators and other experts;
- increased cybersecurity protection costs, which may include the costs of making organizational changes, deploying additional personnel and protection technologies, training employees, and engaging third party experts and consultants;
- increased insurance premiums;
- reputational damage that adversely affects customer or investor confidence;
- damage to the company's competitiveness, stock price, and long-term shareholder value; and
- significantly increase our costs to recover or reproduce the data.

Likewise, we currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidate or any future product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. We rely on these third parties to implement effective security measures and identify and correct for any failures, deficiencies or breaches. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidate or any future product candidates could be hindered or delayed.

We use and generate materials that may expose us to material liability.

Our research programs involve the use of hazardous materials and chemicals, which are currently only handled by third parties. We are subject to foreign, federal, state and local environmental and health and safety laws and regulations governing, among other matters, the use, manufacture, handling, storage and disposal of hazardous materials and waste products. We may incur significant costs to comply with these current or future environmental and health and safety laws and regulations. In addition, we cannot completely eliminate the risk of contamination or injury from hazardous materials and may incur material liability as a result of such contamination or injury. In the event of an accident, an injured party may seek to hold us liable for any damages that result. Any liability could exceed the limits or fall outside the coverage of our workers' compensation, property and business interruption insurance and we may not be able to maintain insurance on acceptable terms, if at all. We currently carry no insurance specifically covering environmental claims.

Risks Related to the COVID-19 Pandemic

Our business could be adversely affected by the effects of health epidemics, and has been impacted by the ongoing COVID-19 pandemic, in regions where we, or third parties on which we rely, have significant manufacturing, analytical laboratory and transportation facilities, concentrations of clinical trial sites or other business operations. The COVID-19 pandemic and any current or new variants of the virus could materially affect our operations, including at our headquarters in the San Francisco Bay Area, and at our clinical trial sites, as well as the business or operations of our manufacturers, CROs or other third parties with whom we conduct business.

Our business could be adversely affected by health epidemics in regions where we have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of third-party manufacturers and CROs upon whom we rely. For example, the ongoing COVID-19 pandemic spread globally. While vaccinations beginning in 2021 allowed for the partial reopening of the economy, new and emerging variants, as well as reduced efficacy of vaccines over time and the possibility that a large number of people decline to get vaccinated or receive booster shots, creates inherent uncertainty as to the future of our business, our industry and the economy in general in light of the pandemic. The extent to which the COVID-19 pandemic impacts our operations or those of our third-party partners will depend on future developments, which remain highly uncertain and cannot be predicted with confidence, including new and emerging variants or the virus which may impact vaccination efforts, mask and vaccine mandates, travel restrictions, and social distancing in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease, and any additional preventative and protective actions that governments take to contain the COVID-19 pandemic or treat its impact, among others.

Additionally, timely enrollment in planned clinical trials is dependent upon clinical trial sites which will be adversely affected by global health matters, such as pandemics. We are conducting clinical trials for our product candidates in geographies which continue to be affected by the COVID-19 pandemic.

Moreover, COVID-19 may also severely affect employees of third-party CROs located in affected geographies that we rely upon to carry out such enrollments and trials. Such events could cause costly delays to our clinical trial activities, which could adversely affect our ability to obtain regulatory approval for and to commercialize our product candidates, increase our operating expenses, and have a material adverse effect on our financial results.

These and other factors arising from the ongoing COVID-19 pandemic could worsen as the pandemic continues to evolve. Any of these factors, and other factors related to any unforeseen disruptions, have had and could continue to have a material adverse effect on our business and our results of operation and financial condition. Further, uncertainty around these and related issues has severely harmed and is expected to continue to severely harm the economy of the United States, which could impact our ability to raise the necessary capital needed to develop and commercialize our product candidates.

General Risk Factors

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by economic and political changes in the location in which we, or our suppliers and vendors, maintain operations. For example, our business may be generally exposed to the impact of political or civil unrest or military action, including the ongoing conflict between Russia and Ukraine and, while we do not have direct exposure to Ukraine, we do have third-party manufacturing partners with locations in Europe. The activities of such manufacturing partners may be impacted based upon the events taking place there. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Our business is affected by macroeconomic conditions, including rising inflation, interest rates and supply chain constraints.

Various macroeconomic factors could adversely affect our business and the results of our operations and financial condition, including changes in inflation, interest rates and overall economic conditions and uncertainties such as those resulting from the current and future conditions in the global financial markets. For instance, rising interest rates have impacted the Company's net income. Recent supply chain constraints have led to higher inflation, which if sustained could have a negative impact on the Company's product development and operations. If inflation or other factors were to significantly increase our business costs, our ability to develop our current pipeline and new therapeutic products may be negatively affected. Interest rates, the liquidity of the credit markets and the volatility of the capital markets could also affect the operation of our business and our ability to raise capital on favorable terms, or at all, in order to fund our operations. Similarly, these macroeconomic factors could affect the ability of our third-party suppliers and manufacturers to manufacture clinical trial materials for our product candidates.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults or non-performance by financial institutions or transactional counterparties, could adversely affect our current and projected business operations and its financial condition and results of operations.

Adverse developments that affect financial institutions, such as events involving liquidity that are rumored or actual, have in the past and may in the future lead to market-wide liquidity problems. For example, on March 10, 2023, Silicon Valley Bank ("SVB") was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation ("FDIC") as receiver. Similarly, on March 12, 2023, Signature Bank and Silvergate Capital Corp. were each swept into receivership. The Department of the Treasury, the Federal Reserve and the FDIC released a statement that indicated that all depositors of SVB would have access to all of their funds after only one business day of closure, including funds held in uninsured deposit accounts, borrowers under credit agreements, letters of credit and certain other financial instruments with SVB, Signature Bank or any other financial institution that is placed into receivership by the FDIC. The U.S. Department of Treasury, FDIC and Federal Reserve Board have announced a program to provide up to $25 billion of loans to financial institutions secured by certain of such government securities held by financial institutions to mitigate the risk of potential losses on the sale of such instruments, widespread demands for customer withdrawals or other liquidity needs of financial institutions for immediately liquidity may exceed the capacity of such program. Although we are not a borrower or party to any such instruments with SVB, Signature or any other financial institution currently in receivership, if Hercules, or any of our future lenders or counterparties to any such instruments were to be placed into receivership, we may be unable to access such funds.

We either hold the vast majority our financial assets in our name and custody them at a third-party financial institution, or we have transferred them out of SVB. Although we have not experienced any adverse impact to our liquidity or to our current and projected business operations, financial condition or results of operations, uncertainty remains over liquidity concerns in the broader financial services industry, and our business, our business partners, or industry as a whole may be adversely impacted in ways that we cannot predict at this time. Inflation and rapid increases in interest rates have led to a decline in the trading value of previously issued government securities with interest rates below current market interest rates. There is no guarantee that the U.S. Department of Treasury, FDIC and Federal Reserve Board will provide access to uninsured funds in the future in the event of the closure of other banks or financial institutions, or that they would do so in a timely fashion.

Although we assess our banking relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors that us, the financial institutions with which we have

credit agreements or arrangements directly, or the financial services industry or economy in general. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry. These factors could involve financial institutions or financial services industry companies with which we have financial or business relationships, but could also include factors involving financial markets or the financial services industry generally.

The results of events or concerns that involve one or more of these factors could include a variety of material and adverse impacts on our current and projected business operations and our financial condition and results of operations. These could include, but may not be limited to, the following:

- Delayed access to deposits or other financial assets or the uninsured loss of deposits or other financial assets;
- Potential or actual breach of contractual obligations that require us to maintain letters or credit or other credit support arrangements;
- Potential or actual breach of financial covenants in our credit agreements or credit arrangements; or
- Termination of cash management arrangements and/or delays in accessing or actual loss of funds subject to cash management arrangements.

In addition, widespread investor concerns regarding the U.S. or international financial systems could result in less favorable commercial financing terms, including higher interest rates or costs and tighter financial and operating covenants, or systemic limitations on access to credit and liquidity sources, thereby making it more difficult for us to acquire financing on acceptable terms or at all. Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws. Any of these impacts, or any other impacts resulting from the factors described above or other related or similar factors not described above, could have material adverse impacts on our liquidity and our current and/or projected business operations and financial condition and results of operations.

We are no longer an "emerging growth company" as defined in the JOBS Act, and the reduced disclosure requirements applicable to emerging growth companies no longer apply to us.

As of June 30, 2021, the market value of our common stock that was held by non-affiliates exceeded $700 million, and as a result, as of December 31, 2021, we no longer qualified as an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As such, we will incur significant additional expenses that we did not previously incur in complying with the Sarbanes-Oxley Act of 2002 and rules implemented by the SEC. As a large accelerated filer, we were subject to certain disclosure requirements that are applicable to other public companies that were not applicable to us as an emerging growth company. These requirements include:

- compliance with the auditor attestation requirements of Section 404;
- compliance 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;
- full disclosure obligations regarding executive compensation; and
- compliance with the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

However, as of the last business day of our second fiscal quarter of 2022, we determined that we requalify as a smaller reporting company and as a non-accelerated filer for the year ended December 31, 2022. We will therefore no longer be required to comply with certain of the items noted above, including but not limited to the auditor attestation requirements of Section 404. If we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources. Additionally, we expect that our loss of "emerging growth company" status will require additional attention from management and will result in increased costs to us, which could include higher legal fees, accounting fees and fees associated with investor relations activities, among others.

Risks Related to an Investment in Our Securities

The market price of our stock may be volatile, and you could lose all or part of your investment.

The trading price of our common stock is likely to be volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. During the year ended December 31, 2022, our stock price has ranged from $8.00 to $54.80. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report on Form 10-K, these factors include:

- developments associated with our license with Amgen, including any termination or other change in our relationship with Amgen;
- the success of competitive products or technologies;
- regulatory actions with respect to our product candidate or any future product candidates or our competitors' product candidates or products;
- results of clinical trials of our product candidate or any future product candidates or those of our competitors;
- actual or anticipated changes in our growth rate relative to our competitors;
- announcements by us or our competitors or collaborators of significant acquisitions, strategic collaborations, joint ventures, collaborations or capital commitments;
- regulatory, legal or payor developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidate or any future product candidates or clinical development programs;
- the results of our efforts to in-license or acquire additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- changes in the structure of healthcare payment systems;
- general economic, industry and market conditions, including the ongoing COVID-19 pandemic;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad (such as the ongoing conflict between Ukraine and Russia, including the sanctions imposed by the United States, the EU and others on Russia and other related parties);
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry and market conditions.

In addition, the stock market in general, and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies, including very recently in connection with the ongoing COVID-19 pandemic, which has resulted in decreased stock prices for many companies notwithstanding the lack of a fundamental change in their underlying business models or prospects. Although the markets recovered, market and industry factors, including potentially worsening economic conditions and other adverse effects or developments relating to inflation, rising interest rates, and the ongoing COVID-19 pandemic, may significantly reduce the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this "Risk Factors" section, could have a dramatic and material adverse impact on the market price of our common stock.

Because of potential volatility in our trading price and trading volume, we may incur significant costs from class action securities litigation.

Holders of stock in companies that have a volatile stock price frequently bring securities class action litigation against the company that issued the stock. We may be the target of this type of litigation in the future. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. A stockholder lawsuit could also divert the time and attention of our management. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and 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 due to error or fraud may occur and not be detected.

If securities or industry analysts do not publish research, or publish inaccurate or unfavorable research, about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend, in part, on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts do not currently, and may never, publish research on our company. If no securities or industry analysts commence coverage of our company or if they cease to cover our company, the trading price for our stock would likely be negatively impacted. In the event that securities or industry analysts initiate coverage, if one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline. In addition, if our operating results fail to meet the forecast of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

Risks Related to Our Charter and Bylaws

Anti-takeover provisions under our organizational documents and Delaware law could delay or prevent a change of control, which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Our fourth amended and restated certificate of incorporation and second amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;

- a prohibition on stockholder action through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of the stockholders may be called only by the board of directors acting pursuant to a resolution approved by the affirmative vote of a majority of the directors then in office, and special meetings of stockholders may not be called by any other person or persons;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds (2/3) of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than a majority of all outstanding shares of our voting stock to amend any bylaws by stockholder action and not less than two-thirds (2/3) of all outstanding shares of our voting stock to amend specific provisions of our certificate of incorporation; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval, which preferred stock may include rights superior to the rights of the holders of common stock.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These anti-takeover provisions and other provisions in our fourth amended and restated certificate of incorporation and second amended and restated bylaws could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors and could also delay or impede a merger, tender offer or proxy contest involving our company. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors of your choosing or cause us to take other corporate actions you desire. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

Our amended and restated bylaws designate the Court of Chancery of the State of Delaware 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, or employees.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of fiduciary duty owed by any of our directors, officers, and employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our second amended and restated bylaws (including the interpretation, validity or enforceability thereof), or (iv) any action asserting a claim that is governed by the internal affairs doctrine(the "Delaware Forum Provision"). The Delaware Forum Provision will not apply to any causes of action arising under the Exchange Act. Our amended and restated bylaws further provide that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (the "Federal Forum Provision"). In addition, our amended and restated bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock is deemed to have notice of and consented to the Delaware Forum Provision and the Federal Forum Provision; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the U.S. federal securities laws and the rules and regulations thereunder.

The Delaware Forum Provision and the Federal Forum Provision in our bylaws may impose additional litigation costs on stockholders in pursuing any such claims. Additionally, these forum selection clauses may limit our stockholders' ability to bring a claim in a judicial forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage the filing of lawsuits against us and our directors, officers and employees, even though an action, if successful, might benefit our stockholders. In addition, while the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court are "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. If the Federal Forum Provision is found to be unenforceable, we may incur

additional costs associated with resolving such matters. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is not enforceable or invalid. The Court of Chancery of the State of Delaware and the federal district courts of the United States may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

Risks Related to Income Taxes

Changes in tax laws could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. It cannot be predicted whether, when, in what form, or with what effective dates, new tax laws may be enacted, or regulations and rulings ay be promulgated or issued under existing or new tax laws, which could result in an increase in our or our stockholders' tax liability or require changes in the manner in which we operate in order to minimize or mitigate any adverse effects of changes in tax law or in the interpretation thereof. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2022, we had U.S. federal and state net operating loss, or NOL, carryforwards of $248.4 million and $235.5 million, respectively and federal and state research and development tax credit carryforwards of $8.9 million and $1.2 million, respectively. If not utilized, such NOL carryforwards (other than federal NOL carryforwards arising in taxable years beginning after December 31, 2017) and research and development credits will expire at various dates beginning in 2037 and 2033, respectively. Our ability to use our U.S. federal and state NOL and tax credit carryforwards to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income. We do not anticipate generating revenue from sales of products for the foreseeable future, if ever, and we may never achieve profitability. These NOL and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under the current law, federal NOL carryforwards generated in tax years beginning after December 31, 2017 are not subject to expiration. However, any such NOL carryforwards may only offset 80% of our annual taxable income in taxable years beginning after December 31, 2020. In addition, under Sections 382 and 383 of the Code, the amount of benefits from our NOL carryforwards may be impaired or limited if we incur a cumulative ownership change of more than 50 percentage points by certain stockholders, as interpreted by the U.S. Internal Revenue Service, over a three-year period. We experienced such ownership changes on March 24, 2017, June 7, 2018 and July 8, 2020. We may experience ownership changes again in the future, some of which may be outside our control. No ownership change occurred in 2022. As a result, our use of federal NOL and tax credit carryforwards could be limited. State NOL carryforwards may be similarly limited. Any such disallowances may result in greater tax liabilities than we would incur in the absence of such a limitation and any increased liabilities could adversely affect our business, results of operations, financial position and cash flows.

Item 1B. Unresolved Staff Comments.

None

Item 2. Properties.

We lease office space where our corporate headquarters are located, which consists of 6,647 square feet located at 601 Gateway Boulevard, South San Francisco, California. We believe our current office space is sufficient to meet our office needs until the expiration of the lease in July 2027.

Item 3. Legal Proceedings.

From time to time, we may be involved in lawsuits, claims, investigations and proceedings, consisting of intellectual property, commercial, employment and other matters which arise in the ordinary course of business. While the outcome of any such proceedings cannot be predicted with certainty, as of December 31, 2022, we were not party to any legal proceedings that we would expect to have a material adverse impact on our financial position, results of operations or cash flow.

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.

On June 20, 2019 our common stock began trading on the Nasdaq Global Select Market under the symbol "AKRO". Prior to such time, there was no public market for our common stock.

Stockholders

As of March 6, 2023, there were 5 stockholders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Recent Sales of Unregistered Securities

During the year ended December 31, 2022, we did not issue or sell any unregistered securities not previously disclosed in an Annual Report on Form 10-K or in a Current Report on Form 8-K.

Dividend Policy

We have never paid or declared any cash dividends on our common stock, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors that our board of directors deems relevant.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report.

Item 6. [Reserved]

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

The following discussion should be read in conjunction with our financial statements and accompanying footnotes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. See "Special Note Regarding Forward-Looking Statements." Because of many factors, including those factors set forth in Part 1, Item 1A "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. 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 law.

Overview

We are a clinical-stage company dedicated to developing transformational treatments for patients with serious metabolic diseases marked by high unmet medical need, including non-alcoholic steatohepatitis, or NASH, a disease without any approved therapies. NASH is a severe form of nonalcoholic fatty liver disease, or NAFLD, characterized by inflammation and fibrosis in the liver that can progress to cirrhosis, liver failure, cancer and death. Our lead product candidate, efruxifermin, or EFX, is an analog of fibroblast growth factor 21, or FGF21, which is an endogenously expressed hormone that protects against cellular stress and regulates metabolism of lipids, carbohydrates and proteins throughout the body. Based on statistically significant fibrosis regression and NASH resolution among patients with biopsy-confirmed pre-cirrhotic NASH, as well as consistent results across multiple clinical trials, we believe EFX has the potential, if approved, to be a best-in-class medicine for treating NASH.

EFX has been evaluated in four randomized, double-blind, placebo-controlled clinical trials, for which results have been reported. In these clinical trials, a total of 244 adult patients with either NASH (N=161) or T2D (N=83) were treated with EFX and evaluated for up to 24 weeks. We recently reported Week 24 results of the Phase 2b HARMONY study in patients with pre-cirrhotic NASH (F2-F3) fibrosis. Both the 50mg and 28mg EFX dose groups achieved statistical significance on primary and secondary histology endpoints after 24 weeks. On the primary endpoint of at least a one-stage improvement of fibrosis without worsening of NASH, the 50mg group (41%) and 28mg group (39%) had a response rate approximately double that of placebo (20%). In addition, 76% of patients treated with 50mg EFX and 47% of those treated with 28mg achieved NASH resolution without worsening of fibrosis, which represented response rates approximately three to five times the placebo rate of 15%. We also observed 41% and 29% response rates for the 50mg and 28mg dose groups, respectively, on a combined endpoint of at least a one-stage improvement in fibrosis and NASH resolution, which were approximately six to eight times the 5% placebo rate. Significant improvements in non-invasive fibrosis markers, liver fat, liver enzymes, lipoproteins, and glycemic control were also observed for both EFX dose groups, with an additional significant reduction in body weight observed for the 50mg dose group. Across EFX groups, the most frequent adverse events were mild gastrointestinal events. We believe these results favorably differentiate EFX within the NASH landscape.

EFX is currently being evaluated in two Phase 2b clinical trials in patients with biopsy-confirmed NASH: a long-term follow-up period for the HARMONY study in patients with pre-cirrhotic NASH (F2-F3 fibrosis), for which we recently reported results after 24 weeks of treatment, and the SYMMETRY study in patients with cirrhotic NASH (F4 fibrosis, compensated). The SYMMETRY study includes an expansion cohort, known as Cohort D, evaluating the safety and tolerability of EFX compared to placebo when added to an existing GLP-1 receptor agonist in patients with pre-cirrhotic NASH (F1-F3 fibrosis) and Type 2 diabetes. We expect to report the results of Cohort D in the second quarter of 2023 and the results of the SYMMETRY study in the fourth quarter of 2023.

Results from the 16-week Phase 2a BALANCED study, which included an expansion cohort of patients who had cirrhosis due to NASH known as Cohort C, as well as the recent results from the 24-week HARMONY study, support our confidence that we will observe statistically significant histological improvements in the SYMMETRY main study evaluating EFX for the treatment of patients with NASH due to cirrhosis. For example, in Cohort C we observed either a one-stage improvement in fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis in 58 percent of EFX-treated patients, compared with 0% for the placebo group, after only 16 weeks of treatment. Response rates for non-invasive markers of fibrosis in Cohort C, which were comparable to the results observed for the BALANCED and HARMONY studies in patients with pre-cirrhotic NASH, are consistent with these

initial histology results.

The FDA has respectively granted Fast Track designation and Breakthrough Therapy Designation, and the EMA has granted PRIME, designation for EFX for the treatment of NASH. The Fast Track and PRIME programs are designed to enhance regulatory support for the development of promising investigational medicines where early clinical data suggest the potential to meet a high unmet medical need. The FDA's Breakthrough Therapy Designation is meant to expedite development and review of a therapy for a serious or life-threatening disease or condition when preliminary clinical evidence indicates the drug may demonstrate substantial improvement on one or more clinically significant endpoints over available therapies. Benefits of these programs may include more frequent regulatory interactions, enhanced guidance on the overall development plan and regulatory strategy, and accelerated assessment of MA applications.

As demonstrated across four separate clinical trials in patients with NASH and/or T2D for which results have been reported, EFX has a unique ability to reproduce the actions of native FGF21. Consequently, we believe EFX holds the potential to be a highly differentiated, best-in-class FGF21 analog and promising monotherapy for the treatment of NASH, if approved. NASH is a complex disease, and its ideal treatment would include intervening at each stage of its pathogenesis. We believe EFX could potentially address all stages of NASH pathogenesis in a single treatment: reversing fibrosis, resolving steatohepatitis, and helping to restore healthy metabolism to the whole body. We also believe EFX may be able to be used in combination with other therapies for potentially greater effect in certain subpopulations, particularly among the substantial proportion of patients with both NASH and T2D who are expected to be treated with GLP-1 therapeutics to manage their T2D.

We were incorporated in January 2017 and have devoted substantially all of our efforts to organizing and staffing our company, business planning, raising capital, in-licensing rights to EFX, research and development activities for EFX, building our intellectual property portfolio, exploring pipeline expansion opportunities, and providing general and administrative support for these operations. To date, we have principally raised capital through the issuance of convertible preferred stock, the initial public offering of our common stock in June 2019, and follow-on public offerings of our common stock in July 2020 and September 2022. In June 2022, we received $25.0 million from an equity investment from Pfizer, Inc. and $10.0 million from a Term Loan provided by Hercules. On March 10, 2023, out of an abundance of caution and to ensure uninterrupted business operations in the face of potential financial sector instability, we drew an incremental $15.0 million from the Term Loan provided by Hercules. We have incurred significant operating losses since inception. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of EFX and any future product candidates. Our net losses were $112.0 million and $100.8 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $422.3 million.

We expect to continue to incur significant expenses for at least the next several years as we advance EFX through later-stage clinical development, develop additional product candidates and seek regulatory approval of any product candidates that complete clinical development. In addition, if we obtain marketing approval for any product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution.

We may also incur expenses in connection with the in-licensing or acquisition of additional product candidates. As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through the sale of equity, debt financings, or other capital sources, which may include collaborations with other companies or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as and when needed, we may have to significantly delay, reduce or eliminate the development and commercialization of one or more of our product candidates or delay our pursuit of potential in-licenses or acquisitions.

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 or maintain profitability. Even if we are able to generate 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 short-term marketable securities of $351.4 million, which we believe will be sufficient to fund our current operating plan into 2025.

Impact of the COVID-19 Pandemic

As of March 2023, the ongoing COVID-19 pandemic continues to evolve. The effects of restrictions previously implemented by the United States, Europe and Asia led to delays in the commencement of non-COVID-19-related clinical trials. As a result, the COVID-19 pandemic has caused significant disruptions to the U.S., regional and global economies and has contributed to significant volatility and negative pressure in financial markets.

We have been carefully monitoring the COVID-19 pandemic and its potential impact on our business and have taken precautionary steps while maintaining business continuity so that we can continue to progress our programs. Our financial results for the years ended December 31, 2022 and 2021 were not significantly impacted by COVID-19. In addition, our ongoing Phase 2b HARMONY trial, for which we reported topline results in September 2022, and our ongoing SYMMETRY trial have not been materially impacted by the COVID-19 pandemic.

Our manufacturing efforts to date have progressed without any adverse impact from COVID-19. Specifically, commercial-scale manufacture of GMP drug substance, or API, and drug product for our Phase 2b HARMONY and SYMMETRY studies was completed during 2020 and 2021. Manufacture of API for Phase 3 clinical trials was initiated on schedule in May 2021 and completed during the first quarter of 2022. Scale-up of manufacturing of a new drug product formulation and delivery device for self-administration by patients in Phase 3 clinical trials was completed in the first quarter of 2022 and manufacture of GMP drug product commenced in the second quarter of 2022. Sufficient drug product/device has been released to support initiation of Phase 3 clinical trials.

Notwithstanding the foregoing, the future impact of the COVID-19 pandemic on our industry, the healthcare system and our current and future operations and financial condition will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the scope, severity and duration of the pandemic, the impact of new strains of the virus, the effectiveness and availability of vaccines and antiviral medications, the pace of these efforts, the actions taken to contain the pandemic or mitigate its impact, any additional preventative and protective actions that governments may direct, and the direct and indirect economic effects of the pandemic and containment measures, among others. See “Item 1A. Risk Factors” for a discussion of the potential adverse impact of COVID-19 on our business, results of operations and financial condition.

Components of our results of operations

Revenue

We have not generated any revenue since our inception and do not expect to generate any revenue from the sale of products in the near future, if at all. If our development efforts for EFX or additional product candidates that we may develop in the future are successful and result in marketing approval or if we enter into collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from such collaboration or license agreements.

Operating expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred in connection with the development of EFX, as well as unrelated discovery program expenses. We expense research and development costs as incurred. These expenses include:

- employee-related expenses, including salaries, related benefits and stock-based compensation expense for employees engaged in research and development functions;
- expenses incurred under agreements with CROs that are primarily engaged in the oversight and conduct of our clinical trials; CMOs that are primarily engaged to provide drug substance and product for our clinical trials, research and development programs, as well as investigative sites and consultants that conduct our clinical trials, nonclinical studies and other scientific development services;

- the cost of acquiring and manufacturing nonclinical and clinical trial materials, including manufacturing registration and validation batches;
- costs related to compliance with quality and regulatory requirements; and
- payments made under third-party licensing agreements.

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. Such amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered.

Product candidates in later stages of clinical development, such as EFX, generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will increase substantially in connection with our planned clinical development activities in the near term and in the future. At this time, we cannot accurately estimate or know the nature, timing and costs of the efforts that will be necessary to complete the clinical development of EFX and any future product candidates.

Our clinical development costs may vary significantly based on factors such as:

- per patient trial costs;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of patients that participate in the trials;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients enrolled in clinical trials;
- potential additional safety monitoring requested by regulatory agencies;
- the duration of patient participation in the trials and follow-up;
- any setbacks or delays to the initiation or completion of preclinical or non-clinical studies, product development or clinical trials due to the COVID-19 pandemic;
- the cost and timing of manufacturing our product candidates, including on account of any disruption or delays to the supply of our product candidates due to the COVID-19 pandemic;
- the phase of development of our product candidates; and
- the efficacy and safety profile of our product candidates.

The successful development and commercialization of product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

- the timing and progress of nonclinical and clinical development activities;
- the number and scope of nonclinical and clinical programs we decide to pursue;
- the ability to raise necessary additional funds;
- the progress of the development efforts of parties with whom we may enter into collaboration arrangements;
- our ability to maintain our current development program and to establish new ones;
- our ability to establish new licensing or collaboration arrangements;
- the successful initiation and completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- the receipt and related terms of regulatory approvals from applicable regulatory authorities;
- the availability of drug substance, drug product, and delivery devices utilized in the production of our product candidate;
- establishing and maintaining agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if our product candidate is approved;
- our ability to obtain and maintain patents, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- our ability to protect our rights in our intellectual property portfolio;
- the commercialization of our product candidate, if and when approved;

- obtaining and maintaining third-party insurance coverage and adequate reimbursement;
- the acceptance of our product candidate, if approved, by patients, the medical community and third-party payors;
- competition with other products;
- the impacts of a pandemic, epidemic or outbreak of an infectious disease, including COVID-19, on the supply of our product candidate and ability to successfully initiate and complete preclinical and non-clinical studies and clinical trials, to receive regulatory approval for our product candidate and to commercialize our product candidate, if approved; and
- a continued acceptable safety profile of our therapy following approval.

A change in the outcome of any of these variables with respect to the development of our product candidates could significantly change the costs and timing associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any of our product candidates.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs for personnel in executive, finance, corporate and business development, and administrative functions. General and administrative expenses also include legal fees relating to patent and corporate matters; professional fees for accounting, auditing, tax and administrative consulting services; insurance costs; administrative travel expenses; marketing expenses and other operating costs.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support development of EFX and our continued research activities. We also anticipate that we will incur increased accounting, audit, legal, tax, regulatory, compliance, and director and officer insurance costs, as well as investor and public relations expenses associated with maintaining compliance with exchange listing and SEC requirements.

Interest expense

Interest expense consists primarily of interest expense on our term loan with Hercules.

Other income

Other income consists primarily of interest income earned on our cash, cash equivalents and short-term marketable securities.

Income taxes

Since our inception, we have not recorded any income tax benefits for the net losses we have incurred in each period or for our earned research and development tax credits, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our net operating loss carryforwards and tax credits will not be realized. As of December 31, 2022, we had U.S. federal and state net operating loss carryforwards of $248.4 million and $235.5 million which may be available to offset future income tax liabilities and expire at various dates beginning in 2037. The federal net operating loss carryforwards include $246.0 million, which may be carried forward indefinitely. As of December 31, 2022, we also had U.S. federal and state research and development tax credit carryforwards of $8.8 million and $1.2 million, respectively, which may be available to offset future tax liabilities which expire at various

dates beginning in 2037 and 2033, respectively. We have recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

Results of operations

Comparison of the 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,			
	2022	2021	$ Change	% Change
	(in thousands, except percentages)			
Operating expenses:				
Research and development	$ 85,284	$ 81,759	$ 3,525	4 %
General and administrative	29,872	19,127	10,745	56 %
Total operating expenses	115,156	100,886	14,270	14 %
Loss from operations	(115,156)	(100,886)	(14,270)	14 %
Interest expense	(739)	—	(739)	— -
Other income, net	3,862	109	3,753	3,443 %
Net loss	$ (112,033)	$ (100,777)	$ (11,256)	11 %

Research and development expenses

The following table summarizes our research and development expenses incurred during the years ended December 31, 2022 and 2021:

	Year Ended December 31,			
	2022	2021	$ Change	% Change
	(in thousands, except percentages)			
Research and development expenses:				
Direct EFX program expenses	$ 66,407	$ 72,336	$ (5,929)	(8) %
Personnel and other R&D related expenses	18,877	9,423	9,454	100 %
Total research and development expenses	$ 85,284	$ 81,759	$ 3,525	4 %

Research and development expenses were $85.3 million and $81.8 million for the years ended December 31, 2022 and 2021, respectively, an increase of $3.5 million. Direct costs for our EFX program decreased $5.9 million, attributed primarily to a $11.1 million increase in CRO expenses related to our ongoing HARMONY and SYMMETRY clinical trials offset by a $16.6 million decrease in third-party contract manufacturing expenses for EFX and a $0.4 million decrease in other research and development costs. Personnel and other research and development related expenses increased $9.5 million, due to a $5.0 million increase in stock-based compensation and a $4.4 million increase in other R&D, wage and wage-related expenses resulting from increased staff. We expect that our research and development expenses will increase substantially in connection with our planned manufacturing and clinical development activities in the near term and in the future to support the ongoing programs.

General and administrative expenses

General and administrative expenses were $29.9 million and $19.1 million for the years ended December 31, 2022 and 2021, respectively, an increase of $10.7 million which was due primarily to a $8.1 million increase in stock-based compensation and a $2.6 increase in other expenses and wage and wage-related expenses resulting from increased staff.

Interest expense

Interest expense the year ended December 31, 2022 is comprised primarily of $0.7 million of interest expense related to the Hercules term loan.

Other income

Other income for the year ended December 31, 2022 is comprised primarily of $3.9 million of interest income from our cash, cash equivalents and short-term marketable securities compared to $0.1 million for the year ended December 31, 2021. This increase is related to increased investment returns on our cash, cash equivalents and short-term and marketable securities.

Liquidity and capital resources

From our inception through December 31, 2022, we have incurred significant operating losses. We have not yet commercialized any products and we do not expect to generate revenue from sales of products for several years, if at all. Through December 31, 2022, we had funded our operations primarily with proceeds from the sale of our redeemable convertible preferred stock, the initial public offering of our common stock in June 2019, and follow-on public offerings of our common stock in July 2020 and in September 2022. In June 2022, we received $25.0 million from an equity investment from Pfizer, Inc. and $10.0 million from a Term Loan provided by Hercules. An additional $15.0 million was borrowed from Hercules on March 10, 2023. From our inception through December 31, 2022, these and other funding sources have provided gross proceeds totaling $677.7 million. As of December 31, 2022, we had cash, cash equivalents and short-term marketable securities of $351.4 million. We have invested our cash resources primarily in liquid money market accounts, commercial paper and corporate debt securities.

The following table summarizes our cash flows for the periods indicated:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
Net cash used in operating activities	$ (92,517)	$ (79,681)
Net cash (used in) provided by investing activities	(63,825)	42,280
Net cash provided by financing activities	255,632	602
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 99,290	$ (36,799)

Cash flows from operating activities

Cash used in operating activities for the year ended December 31, 2022 was $92.5 million, consisting of a net loss of $112.0 million offset by non-cash charges of $24.0 million, including $23.2 million of stock-based compensation expense, and changes in our operating assets and liabilities of $4.5 million. The changes in operating assets and liabilities was primarily related to $2.1 million decrease in prepaid expenses and other assets and $1.0 million increase in accounts payable, all of which are related to the timing of payments and prepayments to our CROs and CMOs for ongoing clinical trial and manufacturing activities. These amounts were partially offset by $7.3 million decreases in accrued expenses and other liabilities mostly related to the timing of prepayments and payments to our CMOs and CROs for ongoing clinical trial and manufacturing activities.

Cash used in operating activities for the year ended December 31, 2021 was $79.7 million, consisting of a net loss of $100.8 million which was partially offset by non-cash charges of $11.4 million and changes in our operating assets and liabilities of $9.7 million. The non-cash charges are primarily related to $10.1 million of stock-based compensation expense and $1.1 million in net amortization of premiums and discounts on short-term marketable securities. The change in operating assets and liabilities was primarily due to increases of $8.7 million in accrued expenses and other current liabilities and $3.3 million in accounts payable, all of which are related to the timing of payments and prepayments to our CROs and CMOs for ongoing clinical trial and manufacturing activities. These amounts were partially offset by an increase of $2.1 million in prepaid expenses and other assets mostly related to the timing of payments and prepayments to our CROs and CMOs for ongoing clinical trial and manufacturing activities and deferred offering costs.

Cash flows from investing activities

Cash used in investing activities for the year ended December 31, 2022 was $63.8 million consisting of $101.4 million used in the purchase of short term securities partially offset by $37.6 million from the maturities of short-term marketable securities.

Cash provided by investing activities for the year ended December 31, 2021 was $42.3 million consisting of $85.8 million from the maturities of short-term marketable securities partially offset by $43.6 million in purchases of short-term marketable securities.

Cash flows from financing activities

Cash provided by financing activities for the year ended December 31, 2022 was $255.6 million, including $216.2 million from follow-on public offering proceeds, net of underwriting discounts, $25.0 million from an equity investment from Pfizer, Inc. through a registered direct common stock offering, $10.0 million from a Term Loan provided by Hercules and $5.3 million in proceeds from the exercise of stock options and the issuance of employee stock purchase plan shares.

Cash provided by financing activities for the year ended December 31, 2021 was $0.6 million from the exercise of stock options and the issuance of employee stock purchase shares.

Description of Indebtedness

We have outstanding borrowings of $10.0 million under a loan and security agreement with Hercules. On March 10, 2023, we borrowed an additional $15.0 million from Hercules and we may borrow an additional $10.0 million at our sole discretion. Upon the occurrence of certain clinical development milestones, an additional $20.0 million may become available to us. In addition, up to an additional $45.0 million may become available to us at Hercules' sole discretion. Borrowings under the loan are repayable in monthly interest-only payments until July 1, 2024, with the option to extend under certain conditions. The interest-only period will be followed by equal monthly payments of principal plus interest until the loan maturity date of January 1, 2027. Outstanding borrowings bear interest at the greater of (i) 7.65% and (ii) the prime rate as reported in the Wall Street Journal plus 3.65%.

Funding requirements

Our primary uses of capital are, and we expect will continue to be, research and development services, compensation and related expenses and general overhead costs. We expect to continue to incur significant expenses and operating losses for the foreseeable future. In addition, since the closing of our IPO, we have incurred and expect to continue to incur additional costs associated with operating as a public company. We anticipate that our expenses will increase significantly in connection with our ongoing activities. The timing and amount of our operating expenditures will depend largely on:

- the initiation, progress, timing, costs and results of nonclinical studies and clinical trials for EFX or any future product candidates we may develop;
- timing delays, if any, with respect to preclinical and clinical development of EFX or any future product candidates we may develop as a result of a pandemic, epidemic or outbreak of an infectious disease, including COVID-19;
- our ability to maintain our license to EFX from Amgen;
- the outcome, timing and cost of seeking and obtaining regulatory approvals from the FDA and comparable foreign regulatory authorities, including the potential for such authorities to require that we perform more nonclinical studies or clinical trials than those that we currently expect or change their requirements on studies or trials that had previously been agreed to;
- the cost to establish, maintain, expand, enforce and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with licensing, preparing, filing, prosecuting, defending and enforcing any patents or other intellectual property rights;
- the effect of competing technological and market developments;
- market acceptance of any approved product candidate, including product pricing, as well as product coverage and the adequacy of reimbursement by third-party payors;

- the cost of acquiring, licensing or investing in additional businesses, products, product candidates and technologies;
- the cost and timing of selecting, auditing and potentially validating a manufacturing site for commercial scale manufacturing;
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval and that we determine to commercialize; and
- our need to implement additional internal systems and infrastructure, including financial and reporting systems.

We expect that we will require additional funding to complete the clinical development of EFX, commercialize EFX, if we receive regulatory approval, and pursue in-licenses or acquisitions of other product candidates. If we receive regulatory approval for EFX or other product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, depending on whether we choose to commercialize EFX ourselves.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, and marketing, distribution or licensing arrangements with third parties. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interest may be materially diluted, and the terms of such securities could include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise 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, we may be required to delay, reduce or eliminate 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 and other commitments

We have entered into agreements with CROs and CMOs to provide services in connection with our nonclinical studies and clinical trials and to manufacture clinical development materials. Apart from the contracts with non-cancelable purchase commitments, we have entered into other contracts in the normal course of business with certain CROs, CMOs, and other third parties for nonclinical research studies and testing, clinical trials and manufacturing services. These contracts do not contain any minimum purchase commitments and are cancelable by us upon prior notice. Payments due upon cancellation consist only of payments for services provided and expenses incurred, including non-cancelable obligations of our service providers, up to the date of cancellation.

Non-cancelable purchase and other arrangements decreased to $8.8 million as of December 31, 2022, compared to $9.3 million as of December 31, 2021. The decrease of $0.5 million was primarily attributable to $0.2 million decrease in the purchase and other obligations to support the growth and expansion of our clinical trials activities and a $0.3 million decrease in operating lease obligations for the office space in South San Francisco, California.

Under the Amgen Agreement, we are obligated to pay Amgen $7.5 million in connection with dosing the first patient in a Phase 3 clinical trial, up to $30.0 million in connection with marketing approvals, and aggregate milestone payments of up to $75.0 million upon the achievement of specified commercial milestones for all products licensed under the agreement. Commencing on the first commercial sale of licensed products, we are obligated to pay tiered royalties on escalating tiers of annual net sales of licensed products ranging from low to high single-digit percentages. The amount and timing of any contingent payment obligations to Amgen are not currently known. The first clinical milestone, in the amount of $2.5 million, was paid to Amgen in August 2019.

Critical accounting policies and estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States or GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, and expenses, as well as related disclosures. 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 to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following critical accounting policies and estimates reflect the most significant judgments and estimates used in the preparation of our consolidated financial statements.

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of these estimates with the service providers and make adjustments, if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors in connection with nonclinical development activities;
- CROs and investigative sites in connection with nonclinical studies and clinical trials; and
- CMOs in connection with the production of nonclinical and clinical trial materials.

We base the expense recorded related to external research and development on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs and CROs that supply, conduct and manage nonclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. 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 or the amount of prepaid expenses 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.

Stock-based compensation

We measure all stock-based awards granted to employees and nonemployees based on the fair value on the date of the grant and recognize compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award, on a straight-line basis. The Company recognizes stock-based compensation expense for awards that contain performance-based conditions using the accelerated attribution method when management determines it is probable that the performance condition will be satisfied. We account for forfeitures as they occur. We estimate the fair value of stock option grants using the Black-Scholes option pricing model. Prior to our initial public offering, the exercise price for all stock options granted was at the estimated fair value of the underlying common stock as determined on the date of grant by our board of directors. Stock-based compensation for restricted stock units is measured based on the market closing price of our common stock on the grant date. Stock-based compensation expense is recognized on a straight-line basis over the requisite service period, generally four years.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the expected stock price volatility, the expected term of the option, the risk-free interest rate for a period that approximates the expected term of the option, and our expected dividend yield. We completed our IPO in June 2019 and accordingly, we lack sufficient

company-specific historical and implied volatility information for our shares traded in the public markets. Therefore, we estimate our expected share price volatility based on the historical volatility of publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The expected term of our stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends on our common stock and do not expect to pay any cash dividends in the foreseeable future. The fair value of each restricted common stock award is estimated on the date of grant based on the fair value of our common stock on that same date.

Compensation expense for purchases under the Employee Stock Purchase Plan is recognized based on the fair value of the common stock estimated based on the closing price of our common stock as reported on the date of offering, less the purchase discount percentage provided for in the plan.

Stock-based compensation expense was $23.2 million and $10.1 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had $36.2 million and $5.5 million of unrecognized stock-based compensation costs related to stock options and Restricted Stock Units (RSUs), which we expect to recognize over a weighted-average period of 2.61 years and 3.94 years for stock options and RSUs, respectively.

We have not recognized, and we do not expect to recognize in the near future, any tax benefit related to stock-based compensation expense as a result of the full valuation allowance on our deferred tax assets including deferred tax assets related to our net operating loss carryforwards.

Recent accounting pronouncements

See Note 2 to our consolidated financial statements included in Part I, Item 1, “Notes to Consolidated Financial Statements,” of this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our business. None of these pronouncements had a material impact on our financial position or results of operations.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Information required by this Item is not applicable as we are electing scaled disclosure requirements available to Smaller Reporting Companies with respect to this Item.

Item 8. Financial Statements and Supplementary Data

AKERO THERAPEUTICS, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the shareholders and the Board of Directors of Akero Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Akero Therapeutics, Inc. (the "Company") as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity (deficit), and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with accounting principles generally accepted in the United States of America.

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.

Critical Audit Matter

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

Accrued Research and Development Expenses & Prepaid Research and Development Expenses — Refer to Note 2 to the financial statements

Critical Audit Matter Description

The Company incurs certain research and development expenses from third-party contract research organizations ("CROs") and contract manufacturing organizations ("CMOs"). The Company recognizes and measures these expenses based on the date on which services commence and the extent of services performed during the applicable reporting period. Depending on the timing of payments to and services provided by the third-parties, the Company recognizes accrued expenses or prepaid expenses.

In estimating the extent of services performed, the Company utilizes information supplied by third-party CROs and CMOs and discussions with Company research and development personnel, pertaining to the progress and status of research and development activities under contract.

We identified accrued and prepaid research and development costs related to CROs and CMOs as a critical audit matter because of the judgments necessary for the Company to estimate the extent of service performed and the associated expense incurred. A high degree of auditor judgment and an increased extent of effort was required when auditing the Company's estimates of the extent of services performed and expenses incurred and evaluating the results of those procedures.

How the Critical Audit Matter Was Addressed in the Audit

Our audit procedures related to accrued and prepaid research and development expenses included the following, among others:

- We evaluated the Company's overall estimation methodology and assumptions as compared to the evidence obtained.
- We tested the design of controls over the estimation of CRO and CMO accrued and prepaid expenses.
- We evaluated publicly available information (such as press releases and investor presentations) and board of directors' materials regarding the status of research and development activities.
- We made selections and tested on a sample basis the accrued and prepaid CRO and CMO balances by:
    - Obtaining and reading the related contracts to understand key provisions and agree them to the Company's analysis.
    - Obtaining and inspecting third-party documents such as service contracts, status reports, and other correspondence received from the vendors related to the services provided and comparing them to the Company's schedule of estimated expenses incurred to date.
    - Testing the mathematical accuracy of the underlying data used in the estimates of the services provided.
    - Inspecting meeting minutes between the Company's finance team and clinical and manufacturing operations and corroborating the progress of research and development activities through inquiry with the Company's clinical operations and manufacturing operations personnel, as well as evaluating third-party vendor information.
- We examined subsequent invoices received from vendors and cash disbursements made subsequent to the balance sheet date and inquired of clinical and manufacturing operations to corroborate the applicable service period in order to evaluate completeness of the accruals.

/s/ Deloitte & Touche LLP

Morristown, NJ

March 17, 2023

We have served as the Company's auditor since 2018.

PART I—FINANCIAL INFORMATION

Item 1. Consolidated Financial Statements

Akero 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	$ 249,773	$ 150,483
Short-term marketable securities	101,676	37,775
Prepaid expenses and other current assets	3,724	5,324
Total current assets	355,173	193,582
Property and equipment, net	47	90
Right of use asset	1,242	1,459
Other assets, noncurrent	108	417
Total assets	$ 356,570	$ 195,548
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 7,968	$ 6,706
Accrued expenses and other current liabilities	11,115	18,422
Total current liabilities	19,083	25,128
Loan payable, noncurrent	9,541	—
Warrant liability	305	—
Operating lease liability, noncurrent	1,079	1,311
Total liabilities	30,008	26,439
Commitments and contingencies (Note 12)		
Stockholders' equity:		
Common stock, $0.0001 par value, 150,000,000 shares authorized as of December 31, 2022 and December 31, 2021; 46,865,206 and 34,900,727 shares issued and outstanding as of December 31, 2022 and December 31, 2021, respectively	5	4
Additional paid-in capital	748,857	479,436
Accumulated other comprehensive income (loss)	37	(27)
Accumulated deficit	(422,337)	(310,304)
Total stockholders' equity	326,562	169,109
Total liabilities and stockholders' equity	$ 356,570	$ 195,548

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

Akero Therapeutics, Inc.

Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)

	Year Ended December 31,	
	2022	2021
Operating expenses:		
Research and development	$ 85,284	$ 81,759
General and administrative	29,872	19,127
Total operating expenses	115,156	100,886
Loss from operations	(115,156)	(100,886)
Interest expense	(739)	—
Other income, net	3,862	109
Net loss	(112,033)	(100,777)
Net unrealized gain (loss) on short-term marketable securities	64	(24)
Comprehensive loss	$ (111,969)	$ (100,801)
Net loss per common share, basic and diluted	$ (2.87)	$ (2.89)
Weighted-average number of shares used in computing net loss per common share, basic and diluted	38,984,772	34,827,385

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

Akero Therapeutics, Inc.

Consolidated Statements of Stockholders' Equity (Deficit)
(In thousands, except share amounts)

	Common Stock		Additional Paid-In-Capital	Accumulated Other Comprehensive Gain (Loss)	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount				
Balances at December 31, 2020	34,741,649	$ 4	$ 468,238	$ (3)	$ (209,527)	$ 258,712
Exercise of stock options	140,128	—	750	—	—	750
Vesting of restricted stock	—	—	21	—	—	21
Issuance of common stock pursuant to ESPP purchases	18,950	—	373	—	—	373
Stock-based compensation expense	—	—	10,054	—	—	10,054
Net unrealized loss on short-term marketable securities	—	—	—	(24)	—	(24)
Net loss	—	—	—	—	(100,777)	(100,777)
Balances at December 31, 2021	34,900,727	$ 4	$ 479,436	$ (27)	$ (310,304)	$ 169,109
Exercise of stock options	559,145	—	5,238	—	—	5,238
Issuance of common stock pursuant to ESPP purchases	33,928	—	280	—	—	280
Issuance of common stock pursuant to equity investment by Pfizer, net of issuance costs	2,525,252	—	24,647	—	—	24,647
Vested warrants issued pursuant to loan agreement	—	—	227	—	—	227
Issuance of common stock upon closing of follow-on public offering, net of issuance costs and underwriting fees of $13,800	8,846,154	1	215,786	—	—	215,787
Stock-based compensation expense	—	—	23,243	—	—	23,243
Net unrealized gain on short-term marketable securities	—	—	—	64	—	64
Net loss	—	—	—	—	(112,033)	(112,033)
Balances at December 31, 2022	46,865,206	$ 5	$ 748,857	$ 37	$ (422,337)	$ 326,562

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

Akero Therapeutics, Inc.

Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2022	2021
CASH FLOWS FROM OPERATING ACTIVITIES		
Net loss	$ (112,033)	$ (100,777)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	23,243	10,054
Depreciation	43	41
Non-cash lease expense	217	203
Net amortization of premiums and discounts on short-term investments	(12)	1,066
Amortization of debt issuance costs and discount	204	—
Fair value change in warrant liability	264	—
Unrealized foreign exchange gain and loss	16	5
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	2,112	(2,101)
Accounts payable	968	3,273
Accrued expenses and other current liabilities	(7,333)	8,737
Operating lease liability	(206)	(182)
Net cash used in operating activities	(92,517)	(79,681)
CASH FLOWS FROM INVESTING ACTIVITIES		
Purchase of short-term marketable securities	(101,446)	(43,561)
Proceeds from maturities of short-term marketable securities	37,621	85,841
Net cash (used in) provided by investing activities	(63,825)	42,280
CASH FLOWS FROM FINANCING ACTIVITIES		
Proceeds from the exercise of stock options	5,016	750
Proceeds from the issuance of common stock pursuant to employee stock purchase plan purchases	280	373
Proceeds from the issuance of common stock pursuant to private offering	25,000	—
Proceeds from the issuance of common stock in a follow-on public offering, net of underwriting costs	216,200	—
Proceeds from loan payable	10,000	—
Payment of loan payable issuance costs	(395)	—
Payment of follow-on public offering issuance costs	(126)	—
Payment of private equity offering costs	(212)	—
Payment of deferred offering costs	(131)	(521)
Net cash provided by financing activities	255,632	602
Net increase (decrease) in cash, cash equivalents and restricted cash	99,290	(36,799)
Cash, cash equivalents and restricted cash at the beginning of the period	150,591	187,390
Cash, cash equivalents and restricted cash at the end of the period	$ 249,881	$ 150,591
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:		
Cash paid for interest	$ 441	$ —
NON-CASH INVESTING AND FINANCING INFORMATION:		
Change in net unrealizable gain (loss) on marketable securities	$ 64	$ (24)
Deferred offering costs reclassified to additional paid-in equity	$ 150	$ —
Equity issuance costs included in accounts payable and accrued expenses and other current liabilities	$ 278	$ —
Deferred offering costs included in accounts payable and accrued expenses and other current liabilities	$ 7	$ —

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

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

1. Nature of the business and basis of presentation

Akero Therapeutics, Inc., together with its wholly owned subsidiary Akero Securities Corporation, ("Akero" or the "Company") is a clinical-stage company dedicated to developing transformational treatments for patients with serious metabolic diseases marked by high unmet medical need, including non-alcoholic steatohepatitis, or NASH, a disease without any approved therapies. NASH is a severe form of nonalcoholic fatty liver disease, or NAFLD, characterized by inflammation and fibrosis in the liver that can progress to cirrhosis, liver failure, cancer and death. The Company's lead product candidate is efruxifermin, or EFX, an analog of fibroblast growth factor 21, or FGF21, which is an endogenously expressed hormone that protects against cellular stress and regulates metabolism of lipids, carbohydrates and proteins throughout the body. EFX is currently being evaluated in two Phase 2b clinical trials in patients with biopsy-confirmed NASH: the HARMONY study in patients with pre-cirrhotic NASH (F2-F3 fibrosis) and the SYMMETRY study in patients with cirrhotic NASH (F4 fibrosis, compensated). The SYMMETRY study includes an expansion cohort, known as Cohort D, evaluating the safety and tolerability of EFX compared to placebo when added to an existing GLP-1 receptor agonist in patients with pre-cirrhotic NASH (F1-F3 fibrosis) and Type 2 diabetes. The Company recently reported Week 24 results from the HARMONY study, which showed statistically significant response rates for both the 50mg and 28mg dose groups on both fibrosis regression and NASH resolution among patients with biopsy-confirmed NASH. Based on these data and data from the BALANCED study, the Company believes EFX has the potential, if approved, to be a best-in-class medicine for treating NASH.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, completion and success of clinical testing, development by competitors of new technological innovations, compliance with governmental regulations, dependence on key personnel and protection of proprietary technology and the ability to secure additional capital to fund operations. EFX will require extensive clinical testing prior to regulatory approval and commercialization. These efforts require significant amounts of additional capital, adequate personnel, and infrastructure and extensive compliance-reporting capabilities. Even if the Company's drug development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company after elimination of all intercompany accounts and transactions. All adjustments necessary for the fair presentation of the Company's consolidated financial statements for the periods presented have been reflected.

Liquidity

In accordance with Accounting Standards Update ("ASU") No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern (Subtopic 205-40)*, the Company has evaluated whether there are certain conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date that the consolidated financial statements are issued.

Since its inception, the Company has funded its operations primarily with proceeds from sales of redeemable convertible preferred stock and with proceeds from its initial public offering ("IPO") in June 2019, a follow-on public offering of its common stock in July 2020 and most recently through a term loan and a registered direct offering in June 2022 and a follow-on public offering in September 2022. The Company has incurred recurring losses since its inception, including net losses of $112,033 and $100,777 for the years ended December 31, 2022 and 2021, respectively. In addition, as of December 31, 2022, the Company had an accumulated deficit of $422,337. The Company expects to continue to generate operating losses for the foreseeable future. As of March 17, 2023, the issuance date of these consolidated financial statements, the Company expects that its existing cash, cash equivalents and short-term marketable securities of $351,449 as of December 31, 2022, will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months from the issuance date of these consolidated financial statements. The Company expects that it will require additional funding to complete the clinical development of EFX, commercialize EFX, if it receives regulatory approval, and pursue in-licenses or acquisitions of other product candidates.

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

2. Summary of significant accounting policies

Use of estimates

The preparation of the Company's consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of expenses during the reporting period. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the recognition of research and development expenses, stock-based compensation expense, warrant liabilities and the valuation allowance for deferred tax assets. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates when there are changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Cash and cash equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the time of purchase to be cash equivalents. Cash equivalents consist primarily of amounts invested in money market accounts.

Short-term marketable securities

The Company invests in short-term marketable securities, primarily money market funds, commercial paper, U.S. treasury securities and corporate debt securities. The Company continually evaluates the credit ratings of its investment portfolio and underlying securities. The Company invests in accordance with its investment policy and invests at the date of purchase in securities with high ratings from top rating agencies. The Company classifies its short-term marketable securities as available-for-sale securities and reports them at fair value in short-term marketable securities on the consolidated balance sheets with related unrealized gains and losses included within accumulated other comprehensive gain (loss) on the consolidated balance sheets. The amortized cost of marketable securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in other income on the consolidated statements of operations and comprehensive loss. When the fair value is below the amortized cost of a marketable security, the Company reviews and determines whether the impairment is due to credit-related factors or noncredit-related factors. The credit-related impairment amount is recognized in other income on the consolidated statements of operations and comprehensive loss, with a corresponding allowance for credit losses account in the consolidated balance sheet. Subsequent improvements in expected credit losses are recognized as a reversal of an amount in the allowance account. If the Company has the intent to sell the security or it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis, then the allowance for the credit loss is written-off and the excess of the amortized cost basis of the asset over its fair value is recorded in the consolidated statements of operations. There were no credit losses recorded during the years ended December 31, 2022 and 2021.

Restricted cash

As of December 31, 2022 and 2021, the Company was required to maintain a separate cash balance of $108 for the benefit of the landlord in connection with the Company’s Gateway office space lease in South San Francisco, California (the “Gateway Lease”), which is classified within other assets (non-current) on the consolidated balance sheets (see Note 12).

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

Concentrations of credit risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist principally of cash, cash equivalents and short-term marketable securities. The Company regularly maintains deposits in accredited financial institutions in excess of federally insured limits. The Company invests its excess cash primarily in money market funds, U.S. treasury notes, and high quality, marketable debt instruments of corporations in accordance with the Company's investment policy. The Company's investment policy defines allowable investments and establishes guidelines relating to credit quality, diversification, and maturities of its investments to preserve principal and maintain liquidity. The Company has not experienced any losses related to its cash equivalents and marketable securities and management believes the Company is not exposed to significant risks of losses.

As of December 31, 2022, the Company held cash deposits at Silicon Valley Bank ("SVB") in excess of government insured limits. On March 10, 2023, SVB was closed by the California Department of Financial Protection and Innovation, and the Federal Deposit Insurance Corporation ("FDIC") was appointed as receiver. No losses were incurred by the Company on deposits that were held at SVB. Management believes that the Company is not currently exposed to significant credit risk as the vast majority of the Company's deposits were either owned directly by the Company and held in custody at a third-party financial institution or, subsequent to March 10, 2023, have been transferred to a third-party financial institution. As of March 17, 2023, the Company has approximately €12,000 on deposit with SVB, which it expects to transfer to another financial institution in the near term. The Company does not currently have any other significant relationships with SVB.

Leases

The Company determines whether an arrangement is or contains a lease at inception by assessing whether the arrangement contains an identified asset and whether the Company has the right to control the identified asset. Right-of-use, or ROU, assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. Lease liabilities are recognized at the lease commencement date based on the present value of future lease payments over the lease term. ROU assets are based on the measurement of the lease liability and are further adjusted by any lease payments made prior to or on lease commencement, lease incentives received and initial direct costs incurred, as applicable. The Company has elected to not recognize leases with a lease term of one year or less on its balance sheet. Operating lease costs included in the measurement of the lease are recognized on a straight-line basis over the lease term. Variable lease costs are expensed as incurred as an operating expense.

The Company determines the lease classification and the present value of future lease payments at the time of the lease commencement using an incremental borrowing rate that it estimates based upon the Company's credit risk and term of the lease. The interest rate implicit in lease contracts has not historically been readily determinable and the Company must therefore use the appropriate incremental borrowing rate to measure its leases. To estimate the incremental borrowing rate, a credit rating applicable to the Company is estimated using a synthetic credit rating analysis since the Company does not currently have a rating agency-based credit rating.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred to discover, research and develop drug candidates, including personnel expenses, stock-based compensation expense, third-party license fees and external costs including fees paid to consultants, contract manufacturing organizations, or CMOs, and clinical research organizations, or CROs, in connection with drug product manufacturing, nonclinical studies and clinical trials, and other related clinical trial fees, such as for investigator grants, patient screening, laboratory work, clinical trial database management, clinical trial material management and statistical compilation and analysis. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are recorded as prepaid expenses. Such amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered.

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

Foreign currency transaction gains and losses related to the purchase of contract manufacturing services are included as a component of research and development expense.

Costs incurred in obtaining technology licenses are charged immediately to research and development expense if the technology licensed has not reached technological feasibility and has no alternative future uses.

Research contract costs and accruals

The Company has entered into various research and development and other agreements with commercial firms, researchers and others for provisions of goods and services. These agreements are generally cancelable, and the related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research and development costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ materially from the Company's estimates.

Stock-based compensation

The Company makes stock-based awards from its stock compensation plans (see Note 7). The Company measures all stock-based awards granted to employees and nonemployees based on the fair value on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award, on a straight-line basis. The Company recognizes stock-based compensation expense for awards that contain performance-based conditions using the accelerated attribution method when management determines it is probable that the performance condition will be satisfied. The Company accounts for forfeitures as they occur. Stock-based compensation for restricted stock units is measured based on the market closing price of our common stock on the grant date. Stock-based compensation expense is recognized on a straight-line basis over the requisite service period, generally four years.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the expected stock price volatility, the expected term of the option, the risk-free interest rate for a period that approximates the expected term of the option, and the Company's expected dividend yield. The Company went public in June 2019 and accordingly, lacks sufficient company-specific historical and implied volatility information for its shares traded in the public markets. Therefore, it estimates its expected share price volatility based on the historical volatility of publicly traded peer companies and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded share price. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends on common stock and does not expect to pay any cash dividends in the foreseeable future. The fair value of each common stock award is estimated on the date of grant based on the fair value of the Company's common stock on that same date.

Compensation expense for purchases under the Employee Stock Purchase Plan is recognized based on the fair value of the common stock estimated based on the closing price of our common stock as reported on the date of offering, less the purchase discount percentage provided for in the plan.

The Company classifies stock-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Loan Payable

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

Loan Payable represents the Loan and Security Agreement ("Loan Agreement") with Hercules Capital, Inc. ("Hercules"), which the Company has accounted for as a debt financing arrangement. Interest expense is accrued using the effective interest rate method over the estimated period the loan will be repaid. Loan issuance costs have been recorded as a debt discount in the consolidated balance sheets and are being amortized and recorded as interest expense throughout the life of the Loan Agreement using the effective interest rate method. The Company considered whether there were any embedded features in the Loan Agreement that require bifurcation and separate accounting as derivative financial instruments pursuant to Accounting Standards Codification ("ASC") Topic 815, Derivatives and Hedging.

Warrant Liabilities

The Company accounts for warrants anticipated to be issued in the future under the Loan Agreement as liabilities and measures them at fair value using the Black-Scholes valuation model. The warrants are subject to remeasurement at each prospective balance sheet date, with any changes in the fair value recorded in the consolidated statements of operations.

Income taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined based on the difference between the consolidated financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Net loss per share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of common stock outstanding during the period, without consideration of common stock equivalents. Diluted net loss per share is the same as basic net loss per share, since the effects of potentially dilutive securities are antidilutive given the Company's net loss.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. The Company's comprehensive loss is comprised of net loss and changes in unrealized gains and losses on its short-term marketable securities.

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Recently adopted accounting pronouncements

In June 2016, the FASB issued ASU No. 2016-13, Financial Instruments - Credit Losses (Topic 326) ("ASU 2016-13"), which introduced a new methodology for accounting for credit losses on financial instruments, including available-for-sale debt securities. The Company adopted ASU 2016-03 as of January 1, 2021. For available-for-sale debt securities with unrealized losses, those losses are recognized as allowances rather than reductions in the amortized cost of the underlying security. The adoption of ASU 2016-03 did not have a material impact on the Company's consolidated financial statements.

In August 2020, the FASB issued ASU No. 2020-06, “Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging— Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity”, or ASU 2020-06. ASU 2020-06 simplifies the accounting for convertible instruments by eliminating the requirement to separate embedded conversion features from the host contract when the conversion features are not required to be accounted for as derivatives under Topic 815, Derivatives and Hedging, or that do not result in substantial premiums accounted for as paid-in capital. The Company adopted ASU 2020-06 on January 1, 2022, on a modified retrospective basis. The adoption of ASU 2020-06 did not have a material impact on the Company's consolidated financial statements.

3. Fair value measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

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The following is a summary of our financial assets and liabilities measured at fair value on a recurring basis as of December 31, 2022 and 2021:

	December 31, 2022			
	Total	Level 1	Level 2	Level 3
Money market funds	$ 137,286	$ 137,286	$ —	$ —
U.S. Treasury securities	58,721	58,721	—	—
Corporate debt securities	5,476	—	5,476	—
U.S. Government agency securities	62,955	—	62,955	—
Commercial paper	27,738	—	27,738	—
Total assets	$ 292,176	$ 196,007	$ 96,169	$ —
Warrant liabilities	$ 305	$ —	$ —	$ 305
Total liabilities	$ 305	$ —	$ —	$ 305

	December 31, 2021			
	Total	Level 1	Level 2	Level 3
Money market funds	$ 116,261	$ 116,261	$ —	$ —
Corporate debt securities	37,775	—	37,775	—
	$ 154,036	$ 116,261	$ 37,775	$ —

Corporate debt securities were valued by the Company using quoted prices in active markets for similar securities, which represent a Level 2 measurement within the fair value hierarchy.

As of December 31, 2022, the Company also held $41,834 in interest-bearing, overnight sweep accounts. This amount approximates its fair value due to the short-term nature of the accounts. The carrying values of the Company's prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair values due to the short-term nature of these assets and liabilities. During the years ended December 31, 2022 and 2021, there were no transfers between Level 1, Level 2 and Level 3.

The Loan Payable is classified as a Level 3 liability. As of December 31, 2022, the carrying value of the Loan Payable, approximates its fair value. The Company estimated the fair value of the warrant liabilities using the Black-Scholes model based on key assumption and inputs (see Note 6). The Company utilizes a probability assessment to estimate the likelihood of vesting for the remaining Loan Agreement warrants and allocated the probability of occurrence percentage to the fair values calculated.

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4. Short-term marketable securities

The following is a summary of short-term marketable securities as of December 31, 2022 and 2021:

	December 31, 2022				
	Amortized cost	Gross unrealized gains	Gross unrealized losses	Credit losses	Fair value
Money market funds	$ 137,286	$ —	$ —	$ —	$ 137,286
U.S. Treasury securities	58,698	23	—	—	58,721
Corporate debt securities	5,478	—	(2)	—	5,476
U.S. Government agency securities	62,939	15	—	—	62,954
Commercial paper	27,739	—	—	—	27,739
	$ 292,140	$ 38	$ (2)	$ —	$ 292,176

Cash equivalents	$ 190,500
Short-term marketable securities	101,676
	$ 292,176

	December 31, 2021				
	Amortized cost	Gross unrealized gains	Gross unrealized losses	Credit losses	Fair value
Money market funds	$ 116,261	$ —	$ —	$ —	$ 116,261
Corporate debt securities	37,802	—	(27)	—	37,775
	$ 154,063	$ —	$ (27)	$ —	$ 154,036

Cash equivalents	$ 116,261
Short-term marketable securities	37,775
	$ 154,036

As of December 31, 2022 and 2021, all of the Company's short-term marketable securities had contractual maturities of less than one year.

5. Accrued expenses and other current liabilities

The following is a summary of accrued expenses and other current liabilities as of December 31, 2022 and 2021:

	December 31, 2022	December 31, 2021
Accrued external research and development expenses	$ 9,789	$ 17,539
Accrued employee compensation and benefits	804	554
Accrued legal and professional fees	197	124
Short-term lease liability and other	325	205
	$ 11,115	$ 18,422

6. Loan Payable and Warrant Liability

On June 15, 2022, the Company entered into a Loan and Security Agreement ("Loan Agreement") with Hercules Capital, Inc. ("Hercules"), for an aggregate principal amount of $100,000 ("Term Loan"). Pursuant to the Loan Agreement, the Term Loan is available to the Company in four tranches, subject to certain terms and conditions.

Under the terms of the Loan Agreement, the Company received $10,000 upon closing, $15,000 was borrowed on March 10, 2023 and an additional $10,000 is available to the Company at its sole discretion. An additional $20,000

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will become available to the Company upon the achievement of certain clinical and financial milestones. An additional $45,000 may become available to the Company at Hercules' sole discretion.

The Term Loan will mature on January 1, 2027 (the “Maturity Date”). The Term Loan bears interest at a variable annual rate equal to the greater of (a) 7.65% and (b) the Prime Rate (as reported in the Wall Street Journal) plus 3.65% (the “Interest Rate”). The Company may make payments of interest only through July 1, 2024, which may be extended to July 1, 2025 upon the achievement of certain milestones (the “interest-only period”). After the interest-only period, the principal balance and related interest will be required to be repaid in equal monthly installments and continuing until the Maturity Date.

The Loan Agreement contains customary closing fees, events of default, and representations, warranties and covenants, including a financial covenant requiring the Company to maintain a minimum cash balance in relation to the outstanding principal balance of the Term Loan. The Loan Agreement provides for a prepayment charge equal to 3% of the outstanding principal balance of the Term Loan if prepayment is made within the first twelve months after closing, 2% if within the second twelve months after closing and 1% thereafter. In addition, the Loan Agreement provides for an End of Term Charge that will be the greater of 5.85% of the outstanding principal balance or $1,170, which is recognized as a debt discount and is being accreted into the amortization of debt issuance costs and discount using the effective interest rate method over the term of the loan payable.

Upon closing, the Company issued warrants to Hercules to purchase shares of the Company’s common stock, par value $0.0001 per share ("common stock"). The number of shares that may be purchased for the Warrants will not exceed 1.5% multiplied by the greater of Tranche I and the aggregate original amount of the term loan advances, divided by the exercise price of the Warrants.

The Company was in compliance with all covenants of the Loan Agreement as of December 31, 2022.

The Company determined in accordance with ASC 480-10 that the initial tranche one advance of $10,000, the additional Term Loan advances available under tranches one, two, three and four and the warrants issued upon closing shall be accounted for as freestanding financial instruments as they are legally detachable and separately exercisable. The Company also determined in accordance with ASC 815-10 that the additional Term Loan advances available under tranches one, two, three and four do not qualify as derivative instruments and that the value associated with these commitments is immaterial.

Upon closing, the Company issued to Hercules warrants to purchase 36,718 shares of Company’s common stock and recognized the initial warrants at their relative fair value of $227 in shareholders equity. In accordance with ASC 815-40, the additional remaining warrants to purchase shares of the Company’s common stock at the closing of the Loan Agreement were recognized at their fair value of $41 as warrant liabilities given the variable settlement amount of the warrant shares. The additional remaining warrants under the Loan Agreement are considered an outstanding instrument at close of the Loan Agreement. The total fair value of $268 associated with these equity and liability classified warrants, is recognized as a debt discount and is being accreted into the amortization of debt issuance costs and discount using the effective interest rate method over the term of the loan payable. The Company reassesses the fair value of the warrant liability at the end of each prospective reporting period. The warrant liabilities were valued at $305 as of December 31, 2022. The change in fair value of the warrant liability of $264 from June 15, 2022 to December 31, 2022 arising from remeasurement was recorded in the statements of operations.

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Future principal debt payments on the currently outstanding loan payable as of December 31, 2022 are as follows (in thousands):

2022	$ —
2023	—
2024	1,710
2025	3,725
2026	4,169
2027	396
Total principal outstanding	10,000
End of term charge	1,170
Total principal outstanding and end of term charge	11,170
Unamortized discount and issuance costs	(1,629)
Loan Payable - noncurrent	$ 9,541

The Company estimated the fair value of the warrant liability as of December 31, 2022 using probability assumptions of achieving the future milestones and using the Black-Scholes model based on the following key assumptions:

	As of December 31, 2022
Expected term (in years)	6.50
Expected volatility	77.29 %
Risk-free interest rate	4.18 %
Expected dividend yield	0.00 %

7. Stockholder's equity (deficit)

Common stock

As of December 31, 2022 and 2021, the Company's certificate of incorporation, as amended and restated, authorized the Company to issue 150,000,000 shares of $0.0001 par value common stock. Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. The holders of common stock, voting exclusively and as a separate class, have the exclusive right to vote for the election of directors of the Company. Common stockholders are entitled to receive dividends, as may be declared by the board of directors. Through December 31, 2022, no cash dividends had been declared or paid.

On June 24, 2019, the Company completed its IPO at which time the Company issued 6,612,500 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 862,500 additional shares of common stock, at a public offering price of $16.00 per share. The Company received $98,394, net of underwriting discounts and commissions, but before deducting offering costs paid by the Company, which were $2,942. Upon the closing of the IPO, all outstanding shares of convertible preferred stock converted into 21,056,136 shares of common stock.

On July 10, 2020, the Company completed a follow-on public offering at which time the Company issued 6,012,390 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 784,224 additional shares of common stock, at a public offering price of $36.00 per share. The Company received $203,460 net of underwriting discounts and commissions, but before deducting offering costs paid by the Company.

On May 18, 2021, the Company filed a Form S-3 Registration Statement and the accompanying prospectus activating an At-The-Market, or ATM, facility by entering into a sales agreement with J.P. Morgan Securities LLC, relating to shares of the Company's common stock offered. Pursuant to the terms of the sales agreement, the Company may offer and sell shares of common stock, having an aggregate price of up to $100,000, from time to time. The

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Company reserved 5,000,000 shares of common stock related to the ATM offering. During the year ended December 31, 2022, the Company did not make any sales under the ATM facility.

On June 15, 2022, the Company entered into a securities purchase agreement for the sale of 2,525,252 shares of the Company's common stock to Pfizer Inc. at $9.90 per share in a registered direct offering conducted without an underwriter or placement agent and pursuant to the Company's effective shelf registration statement on Form S-3ASR and a related prospectus supplement filed with the SEC. The offering closed on June 17, 2022, for net proceeds of $24,647, after deducting offering costs paid by the Company.

On September 19, 2022, the Company completed a follow-on public offering at which time the Company issued 8,846,154 shares of common stock, including the exercise in full by the underwriters of their option to purchase up to 1,153,846 additional shares of common stock, at a public offering price of $26.00 per share. The Company received $216,200 net of underwriting discounts and commissions of $13,800, but before deducting offering costs incurred by the Company.

As of December 31, 2022 and 2021, there were 46,865,206 and 34,900,727 shares of common stock issued and outstanding, respectively.

The following shares of common stock were reserved for issuance as follows:

	December 31, 2022	December 31, 2021
Options outstanding under the 2018 Stock Option and Grant Plan	1,633,173	2,011,891
Options outstanding under the 2019 Stock Option and Incentive Plan	4,146,831	3,209,203
Restricted stock units outstanding under the 2019 Stock Option and Incentive Plan	129,131	—
Warrants to purchase common stock associated with Loan Agreement	36,718	—
Options available for future grant	2,038,142	1,889,299
Warrants available for future grant	146,880	—
Common stock available for ATM program	5,000,000	5,000,000
2019 Employee Stock Purchase Plan	1,187,508	872,429
	14,318,383	12,982,822

Undesignated preferred stock

The Company's fourth amended and restated certificate of incorporation authorizes the Company to issue up to 10,000,000 shares of undesignated preferred stock, par value $0.0001 per share. There were no undesignated preferred shares issued or outstanding as of December 31, 2022.

Warrants Associated with Loan Agreement

In connection with the entry into the Loan Agreement, the Company issued to Hercules warrants to purchase shares of the Company's common stock. The amount of shares that may be purchased for the Warrants will not exceed 1.5% multiplied by the greater of Tranche I and the aggregate original amount of the term loan advances, divided by the exercise price of the Warrants. Upon execution of the Loan Agreement, the Company issued 36,718 warrants to purchase shares of the Company's common stock and recorded the initial warrants at their relative fair value in shareholder's equity.

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8. Stock-based awards

2018 Stock option and grant plan

The Company's 2018 Stock Option and Grant Plan (the "2018 Plan") provided for the Company to grant incentive stock options or nonqualified stock options, restricted stock awards and other stock-based awards to employees, directors and consultants of the Company. The 2018 Plan was administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting and other restrictions were determined at the discretion of the board of directors, or its committee if so delegated.

The total number of shares of common stock that could have been issued under the 2018 Plan was 3,071,960 shares, of which 107,635 shares remained available for grant on June 18, 2019, the date that the Company's 2019 Stock Option and Incentive Plan (the "2019 Plan") became effective. Upon the effectiveness of the 2019 Plan, the 107,635 remaining shares available under the 2018 Plan were transferred and became available for issuance under the 2019 Plan. Shares of common stock underlying outstanding awards under the 2018 Plan that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) will be added to the shares of common stock available for issuance under the 2019 Plan.

2019 Stock option and incentive plan

The 2019 Plan was adopted and approved by the Company's board of directors in May 2019 and by the Company's stockholders in June 2019. The 2019 Plan became effective on June 18, 2019 and replaced the Company's 2018 Plan on that date. The 2019 Plan allows the board of directors or the compensation committee of the board of directors to make equity-based incentive awards to the Company's officers, employees, directors or other key persons (including consultants). The number of shares initially reserved for issuance under the 2019 Plan was 2,572,457, which included the 107,635 shares transferred from the 2018 Plan, and shall be cumulatively increased on each January 1 by 4% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by the Company's board of directors or compensation committee of the board of directors. The 2019 Plan was increased by 1,389,665 shares on January 1, 2021 and by 1,396,029 shares on January 1, 2022.

The 2019 Plan is administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting and other restrictions are determined at the discretion of the board of directors, or its committee if so delegated, except that the exercise price per share of stock options may not be less than 100% of the fair market value of the share of common stock on the date of grant and the term of stock option may not be greater than ten years. All incentive options granted to any person possessing more than 10% of the total combined voting power of all classes of shares may not have an exercise price of less than 110% of the fair market value of the common stock on the grant date. Stock options granted to employees, officers, members of the board of directors and consultants will typically vest over a four-year period.

Shares that are expired, terminated, surrendered or canceled under the 2019 Plan without having been fully exercised will be available for future awards.

2019 Employee stock purchase plan

The 2019 Employee Stock Purchase Plan (the "2019 ESPP") was adopted and approved by the Company's board of directors in May 2019 and by the Company's stockholders in June 2019. The 2019 ESPP became effective on June 18, 2019, at which time 273,869 shares were reserved for issuance. The 2019 ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2020 and each January 1 through January 1, 2029, by the least of (i) 1% of the outstanding number of shares of the Company's common stock on the immediately preceding December 31, (ii) 410,803 shares or (iii) such number of shares as

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determined by the compensation committee. The 2019 ESPP was increased by 347,416 shares on January 1, 2021 and by 349,007 shares on January 1, 2022.

Stock option valuation

The assumptions that the Company used to determine the grant-date fair value of stock options granted to employees, directors and consultants as follows, presented on a weighted average basis:

	Year Ended December 31,	
	2022	2021
Expected term (in years)	5.30	5.77
Expected volatility	74.59 %	72.17 %
Weighted average risk-free interest rate	2.71 %	1.19 %
Expected dividend yield	0.00 %	0.00 %

Stock options

The following table summarizes the Company's stock option activity since December 31, 2021:

	Number of Options	Weighted-Average Exercise Price per Share	Weighted-Average remaining contractual term (years)	Aggregate Intrinsic Value (000's)
Balance outstanding, December 31, 2021	5,221,094	$ 15.49	8.20	36,168
Options granted	1,355,673	$ 28.76		
Options exercised	(559,145)	$ 9.37		
Options cancelled	(237,618)	$ 23.09		
Balance outstanding, December 31, 2022	5,780,004	$ 18.88	7.80	$ 207,611
Vested and expected to vest, December 31, 2022	5,780,004	$ 18.88	7.80	$ 207,611
Exercisable, December 31, 2022	3,670,458	$ 14.37	7.19	$ 148,416

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock.

The weighted average grant-date fair value per share of stock options granted during the years ended December 31, 2022 and 2021 was $28.76 and $13.98, respectively.

Awards with performance-based vesting conditions granted under the 2019 Plan

In December 2021, the Company granted 610,546 stock options to management at an exercise price of $21.10, which vest upon the achievement on or before December 31, 2022 of three pre-determined milestones regarding progress related to the HARMONY study, progress related to the SYMMETRY study, and progress related to availability of drug product for use in Phase 3 clinical trials. One-third of the options vest upon achievement of each of the milestones. In January 2022, the Company granted an additional 248,376 stock options to Company employees with the same performance-based milestones and vesting terms at an exercise price of $21.70. In September 2022, two of the three performance-based awards milestones were achieved and were deemed vested. In December 2022, the third portion of the performance-based awards milestones was achieved and was deemed vested. During the year ended December 31, 2022, the Company recognized $10,487 of related stock compensation expense, based upon management's estimates of the probabilities of the milestones being achieved and the fully vesting of the performance awards.

Restricted Stock Units

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The 2019 Plan allows for the grants of Restricted Stock Units (RSUs). Generally, the RSUs are subject to a four-year vesting period of which the Company has designated to vest on a quarterly basis over the remaining vesting term. In December 2022, the Company granted 129,131 RSUs to executive management with a total grant date fair value of $5,546. As of December 31, 2022, these awards are not yet vested.

The following table summarizes the Company's RSUs activity since December 31, 2021:

	Underlying shares	Weighted-Average Grant Date Fair Value per Share	Weighted-Average remaining contractual term (years)	Aggregate Intrinsic Value (000's)
Balance outstanding, December 31, 2021	—	$ —	—	—
Granted	129,131	$ 42.95		
Vested	—	$ —		
Cancelled or forfeited	—	$ —		
Balance outstanding, December 31, 2022	129,131	$ 42.95	2.07	$ 7,076

Stock-based compensation

The following table summarizes the Company's stock-based compensation expense during the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
Classified within research and development expense	$ 8,096	$ 3,054
Classified within general and administrative expense	15,147	7,000
Total stock-based compensation expense	$ 23,243	$ 10,054

As of December 31, 2022, total unrecognized compensation cost related to unvested stock options and RSUs was $36,164 and 5,461, respectively. These unvested stock options and RSUs are expected to be recognized over a weighted average period of 2.61 years and 3.94 years respectively.

9. Amgen license agreement

In June 2018, the Company entered into a license agreement (the "Amgen Agreement") with Amgen, Inc. ("Amgen") pursuant to which the Company was granted an exclusive license to certain patents and intellectual property related to a long-acting FGF21 analog in order to commercially develop, manufacture, use and distribute FGF21 as a treatment for NASH and other serious metabolic diseases. The Amgen Agreement provides the Company with exclusive global rights to the licensed products and the right to grant sublicenses that cover EFX to third parties.

In exchange for these rights, the Company made an upfront payment of $5,000 and issued 2,653,333 shares of Series A Preferred Stock with a fair value of $1,353 to Amgen. Amgen was also entitled to maintain a 10% ownership interest of the outstanding shares of the Company's common stock, on a fully diluted and converted basis, through the second closing of the Company's Series A Preferred Stock financing. In November 2018, in connection with the second closing of the Company's Series A Preferred Stock financing, the Company issued 3,205,128 shares of Series A Preferred Stock to Amgen for a total value of $7,404, satisfying its anti-dilution obligation under the Amgen Agreement.

Under the Amgen Agreement, the Company made a milestone payment in the third quarter of 2019 of $2,500 in connection with dosing the first patient in the BALANCED study and is obligated to pay Amgen $7,500 in connection with dosing the first patient in a Phase 3 clinical trial, up to $30,000 in connection with marketing approvals, and aggregate milestone payments of up to $75,000 upon the achievement of specified commercial milestones for all products licensed under the Amgen Agreement.

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Under the Amgen Agreement, the Company is obligated to pay Amgen tiered royalties ranging from a low to high single-digit percentages on annual net sales of the licensed products, beginning on the first commercial sale of such licensed products in each country and expiring on a country-by-country basis on the latest of (i) the expiration of the last valid patent claim covering such licensed products in such country, (ii) the loss of regulatory exclusivity in such country, and (iii) ten years after the first commercial sale of such licensed product in such country. The royalty payments are subject to reduction under specified conditions set forth in the Amgen Agreement.

The Company is solely responsible for all development, manufacturing, and commercial activities and costs of the licensed products, including clinical studies or other tests necessary to support the use of a licensed product. The Company is also responsible for costs related to the filing, prosecution and maintenance of the licensed patent rights.

The Amgen Agreement will remain in effect until the expiration of the royalty term in all countries for all licensed products. The Amgen Agreement may be terminated by either party with at least 90 days' notice in the event of material breach by the other party that remains uncured for 90 days, by either party for insolvency or bankruptcy of the other party and immediately by Amgen if the Company challenges the licensed patents. The Company may also terminate the Amgen Agreement with 90 days' written notice for discretionary reasons such as scientific, technical, regulatory or commercial issues, as defined in the Amgen Agreement.

During the years ended December 31, 2022 and 2021, the Company did not record any research and development expense in connection with the Amgen Agreement.

10. Income taxes

During the years ended December 31, 2022 and 2021, the Company recorded no income tax benefits for the net operating losses incurred or for the research and development tax credits generated in each period due to its uncertainty of realizing a benefit from those items. All of the Company's operating losses since inception have been generated in the United States.

A summary of the Company's current and deferred tax provision is as follows:

	Year Ended December 31,	
	2022	2021
Current income tax provision:		
Federal	$ —	$ —
State	—	—
Total current income tax provision	—	—
Deferred income tax benefit:		
Federal	27,269	23,352
State	14,568	7,274
Total deferred income tax benefit	41,837	30,626
Change in deferred tax asset valuation allowance	(41,837)	(30,626)
Total provision for income taxes	$ —	$ —

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A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,			
	2022		2021	
Federal statutory income tax rate	21.0	%	21.0	%
State income taxes, net of federal benefit	13.0		7.2	
Research and development tax credits	2.4		2.0	
Other permanent differences	0.8		(0.1)	
Change in deferred tax asset valuation allowance	(37.2)		(30.1)	
Effect of Section 382 limitation	-		-	
Effective income tax rate	-	%	-	%

Net deferred tax assets as of December 31, 2022 and 2021 consisted of the following:

	December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carry forwards	$ 68,450	$ 56,128
Research and development tax credit carry forwards	7,704	4,522
License fees	3,355	3,523
Stock based compensation	8,974	3,716
Capitalized research and experimentation costs	20,803	—
Accruals, reserves and other	191	151
	109,477	68,040
Valuation allowance	(108,690)	(66,853)
Net deferred tax assets	787	1,187
Deferred tax liabilities:		
Prepaid expenses	(787)	(1,187)
Net deferred tax liabilities	(787)	(1,187)

As of December 31, 2022, the Company had U.S. federal and state net operating loss carryforwards of $248,406 and $235,472, respectively, which may be available to offset future taxable income and begin to expire in 2037. The federal net operating loss carryforwards include $245,963, which may be carried forward indefinitely. As of December 31, 2022, the Company also had U.S. federal and state research and development tax credit carryforwards of $8,827 and $1,249, respectively, which may be available to offset future tax liabilities and begin to expire in 2033. During the year ended December 31, 2022, gross deferred tax assets, before valuation allowance, increased by $41,837, due to the operating loss incurred by the Company during that period.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income or tax liabilities. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The annual limitation is determined by multiplying the value of the Company's stock at the time of such ownership change by the applicable long-term tax-exempt rate. Such limitations may result in expiration of a portion of the NOL carryforwards before utilization. As of December 31, 2022, the Company determined that ownership changes occurred on March 24, 2017, June 7, 2018 and July 8, 2020. As a result of the ownership changes, approximately $2,118 and $3,632 of the NOLs will expire unutilized for federal and state purposes, respectively. The ability of the Company to use its remaining NOL carryforwards may be further limited if the Company experiences a Code Section 382 ownership change as a result of future changes in its stock ownership.

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

The Company's research and development credits are subject to Code Section 383 and are limited due to the ownership changes that the Company has experienced. As of December 31, 2022, the Company has derecognized approximately $87 and $43 of gross federal and state research and development credits, respectively. The Company has not derecognized any of the California research and development credit-related deferred tax assets because the credits do not expire.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets at each reporting period. In doing so, the Company has considered its history of cumulative net losses incurred and its lack of commercialization of any products or generation of any revenue from product sales and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been recorded against the net deferred tax assets as of December 31, 2022 and 2021. Management reevaluates the positive and negative evidence at each reporting period.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2022 and 2021 related primarily to the increase in net operating loss carryforwards and research and development tax credit carryforwards and were as follows:

	2022	2021
Valuation allowance as of January 1,	$ (66,853)	$ (36,227)
Increases recorded to income tax provision	—	—
Decreases recorded as a benefit to income tax provision	(41,837)	(30,626)
Valuation allowance as of December 31,	$ (108,690)	$ (66,853)

As of December 31, 2022, the Company had gross unrecognized tax benefits of $2,110, none of which if recognized, would reduce the effective tax rate in a future period, due to the Company's full valuation allowance on U.S. net deferred tax assets. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision. As of December 31, 2022, the Company had not accrued interest or penalties related to uncertain tax positions and no amounts had been recognized in the Company's consolidated statements of operations and comprehensive loss. For the year ended December 31, 2022, the Company will file income tax returns in the U.S., California, Connecticut, Florida, Illinois, Massachusetts, Maryland, New York, New Jersey, North Carolina, Pennsylvania and Virginia, as prescribed by the tax laws of the jurisdictions in which it operates. The Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. The Company is open to future tax examination under statute from 2018 to the present.

A reconciliation of the beginning and ending unrecognized tax benefits for the years ended December 31, 2022 and 2021 is as follows

Balance at December 31, 2020	$ 644
Increases related to prior year tax positions	66
Increases related to current year tax positions	603
Balance at December 31, 2021	1,313
Increases related to prior year tax positions	51
Increases related to current year tax positions	746
Balance at December 31, 2022	$ 2,110

On March 27, 2020, the "Coronavirus Aid, Relief and Economic Security (CARES) Act" (the "Act") was signed into law. The Act includes provisions relating to refundable payroll tax credits, deferment of the employer portion of certain payroll taxes, net operating loss carryback periods, alternative minimum tax credit refunds, modifications to the net interest deduction limitations and technical corrections to tax depreciation methods for qualified improvement property. The Company analyzed the provisions of the Act and determined there was no significant impact to its income taxes for the year ended December 31, 2022.

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

On June 29, 2020, California Governor signed Assembly Bill 85 ("A.B. 85"), which now becomes California law. A.B. 85, which includes several tax measures, provides for a three-year suspension of the use of net operating losses for medium and large businesses and a three-year cap on the use of business incentive tax credits to offset no more than $5,000 of tax per year. Generally, A.B. 85 suspends the use of net operating losses for taxable years 2020, 2021, and 2022 for taxpayers with taxable income of $1,000 or more." On February 9, 2022, the California Governor signed into law CA SB 113 which shortens the previously enacted suspension on the use of NOLs and R&D credits. Accordingly, SB 113 restored NOL utilization and removes the R&D credit limitation for 2022, and as such no impact to the Company for the period ended December 31, 2022.

The Tax Cuts and Jobs Act ("TCJA") included a change in the treatment of research and development expenditures for tax purposes under Section 174. Effective for tax years beginning after December 31, 2021, specified R&D expenditures must undergo a 5-year amortization period for domestic spend and a 15-year amortization period for foreign spend, beginning with the midpoint of the taxable year in which such expenditures are paid or incurred. Prior to the effective date (2021 tax year and prior), taxpayers were able to immediately expense R&D costs under Section 174(a) or had the option to capitalize and amortize R&D expenditures over a 5-year recovery period under Section 174(b). Accordingly, the Company is estimating 2022 capitalization of U.S R&D expenditures net of 2022 amortization of approximately $57,658 (an addback to estimated 2022 US taxable income). Additionally, the requirement to capitalize and amortize foreign R&D expenses over 15 years resulted in 2022 capitalization of R&D expenditures (net of amortization) of $14,728.

On August 16, 2022, the IRA was signed into law. The IRA includes implementation of a new alternative minimum tax, an excise tax on stock buybacks, and significant tax incentives for energy and climate initiatives, among other provisions. The Company is evaluating the provisions included under the IRA and does not expect the provisions to have a material impact to the Company's consolidated financial statements.

All tax returns will remain open for examination by the federal and state taxing authorities for three and four years, respectively, from the date of utilization of any net operating loss carryforwards or research and development credits.

11. Net loss per share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows:

	Year Ended December 31,	
	2022	2021
Numerator:		
Net loss	$ 112,033	$ 100,777
Denominator:		
Weighted average common shares outstanding, basic and diluted	38,984,772	34,827,385
Net loss per share, basic and diluted	$ 2.87	$ 2.89

The Company excluded nil shares and 8,127 shares of restricted common stock, presented on a weighted average basis, from the calculations of basic net loss per share for the years ended December 31, 2022 and 2021, respectively, because those shares had not vested.

The Company's potentially dilutive securities, which include stock options, warrants and unvested restricted common stock, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share is the same. The Company excluded the following potential common shares,

(Amounts in thousands, except share and per share data)

presented based on amounts outstanding at each period end, from the computation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect:

	Year Ended December 31,	
	2022	2021
Options to purchase common stock	5,780,004	5,221,094
Unvested restricted stock units	129,131	—
Warrants to purchase common stock	36,718	—
Warrants available for future grant	146,880	—
	6,092,733	5,221,094

12. Commitments and contingencies

COVID-19 Pandemic

In December 2019, a novel strain of coronavirus ("COVID-19") was reported to have surfaced in Wuhan, China and subsequently spread to other countries, including Europe and the United States, and was declared a pandemic by the World Health Organization. Despite progress with distribution and administration of vaccines, COVID-19 and its effects continue to evolve and countries including the United States, Europe and Asia continue to respond by implementing restrictions such as travel restrictions, social distancing requirements, stay-at-home orders and delayed commencement of non-COVID-19-related clinical trials. The Company's financial results for the years ended December 31, 2022 and 2021 were not significantly impacted by COVID-19, however, the Company cannot at this time predict the specific extent, duration, or full impact that the ongoing COVID-19 pandemic will have on its financial condition, operations, and business plans for 2022, including the timing and enrollment of patients in its planned clinical trials and other expected milestones of its product candidate.

Operating lease

In February 2020, the Company entered into a seven-year agreement to occupy 6,647 square feet of office space in South San Francisco, California. The lease commenced on July 10, 2020 when the Company took occupancy of the leased space and the lease was determined to be operating classified. Under the agreement, the Company is required to make approximately $2,300 in total minimum payments during the term. The Company is also required to pay its proportionate share of building operating and tax costs after the first year under lease which are not included in the measurement of the lease and treated as variable lease cost and expensed when incurred.

As of December 31, 2022, maturities of the Company's operating lease liability was as follows:

2023	321
2024	331
2025	341
2026	351
2027	208
Total future minimum lease payments	1,552
Less imputed interest	(242)
Present value of operating lease liabilities	$ 1,310

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

As of December 31, 2022, the total lease liability was $1,310, of which $1,079 was noncurrent and $231 was short-term and classified within "Accrued expenses and other current liabilities" on the consolidated balance sheet.

For the years ended December 31, 2022 and 2021, the components of operating lease cost were as follows:

		Year Ended December 31,	
		2022	2021
Lease cost:	Statement of Operations Classification:		
Operating lease cost	General and administrative expense	$ 324	$ 324
Short-term lease cost	General and administrative expense	58	—
Variable operating lease cost	General and administrative expense	58	17
Total operating lease cost		$ 440	$ 341
Other information:			
Cash paid for amounts included in the measurement of operating lease liability		$ 312	$ 303
Weighted average remaining lease term		4.6	5.6
Weighted average discount rate		7.6%	7.6%

Research and manufacturing and other commitments

The Company has entered into agreements with contract research organizations and contract manufacturing organizations to provide services in connection with its nonclinical studies and clinical trials and to manufacture clinical development materials. As of December 31, 2022, the Company had non-cancelable purchase and other commitments under these agreements totaling $7,239.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, 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. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not currently aware of any indemnification claims and has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2022.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses as incurred the costs related to such legal proceedings.

Akero Therapeutics, Inc.

Notes to Consolidated Financial Statements
(Amounts in thousands, except share and per share data)

13. Subsequent event

The Company evaluated subsequent events through March 17, 2023, the date on which these consolidated financial statements were issued. On Friday, March 10, 2023, the Company drew an incremental $15,000 from its term loan facility with Hercules to ensure no interruption to near-term business operations in the face of potential volatility in the financial sector. In connection with the draw of additional funds, the Company's existing warrants to purchase shares of common stock held by Hercules became exercisable for 45,898 shares of common stock.

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

None

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation and supervision of our Chief Executive Officer and our Chief Financial Officer, have 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 December 31, 2022 on Form 10-K. Disclosure control and procedures include, without limitation, controls and procedures designed to ensure that information we are required to disclose in reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in SEC rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure.

Based on that evaluation, our Chief Executive Officer and our Chief Financial Officer have concluded that, as of the end of December 31, 2022, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

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 designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of consolidated financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the company;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the company's assets that could have a material effect on the financial statements.

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

Under the supervision and with the participation of management and our Chief Executive Officer and our Chief Financial Officer, we evaluated the effectiveness of our internal control over financial reporting as of December 31, 2022, based on the framework set forth by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO") in Internal Control—Integrated Framework (2013 Framework). Based on the results of our evaluation under that framework, we concluded that our internal control over financial reporting was effective as of December 31, 2022.

As a smaller reporting company, our independent registered accounting firm is not required to issue an attestation report on our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitation on the Effectiveness of Internal Control.

The effectiveness of any system of internal control over financial reporting, including ours, is subject to inherent limitations, including the exercise of judgment in designing, implementing, operating, and evaluating the controls and procedures, and the inability to eliminate misconduct completely. Accordingly, any system of internal control over financial reporting, including ours, no matter how well designed and operated, can only provide reasonable, not absolute assurances. In addition, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. We intend to continue to monitor and upgrade our internal controls as necessary or appropriate for our business but cannot assure you that such improvements will be sufficient to provide us with effective internal control over financial reporting.

Item 9B. Other Information.

On Friday, March 10, 2023, the Company drew an incremental $15.0 million from its loan facility with Hercules Capital ("Hercules"). In connection with the draw of additional funds, the Company's existing warrants to purchase shares of common stock held by Hercules became exercisable for 45,898 shares of common stock.

Item 9C: Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Except as set forth below, the information required by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2022.

We have adopted a Code of Business Conduct and Ethics that applies to all of our directors, officers and employees, including our principal executive officer and principal financial officer. The Code of Business Conduct and Ethics is posted on our website at https://ir.akerotx.com/corporate-governance/documents-charters.

We intend to satisfy the disclosure requirement under Item 5.05 of Form 8-K regarding an amendment to, or waiver from, a provision of this Code of Business Conduct and Ethics by posting such information on our website, at the address and location specified above and, to the extent required by the listing standards of The NASDAQ Global Select Stock Market, by filing a Current Report on Form 8-K with the SEC, disclosing such information.

Item 11. Executive Compensation.

The information called for by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2022.

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

The information called for by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2022.

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

The information called for by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2022.

Item 14. Principal Accounting Fees and Services

The information called for by this item is incorporated by reference from our definitive Proxy Statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2022.

Part IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are filed as part of this Annual Report on Form 10-K:

1) The consolidated financial statements filed as part of this Annual Report on Form 10-K are listed in the "Index to Consolidated Financial Statements" under Part II, Item 8 of this Annual Report on Form 10-K.

2) No schedules are submitted because they are not applicable, not required or because information is included in the consolidated financial statements or the notes thereto.

3) The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

Item 16. Form 10-K Summary

The Company has elected not to include summary information.

EXHIBIT INDEX

Exhibit Number	Exhibit Description
3.1	Fourth Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 of the Registrant's Current Report on Form 8-K (File No. 001-38944) filed on June 24, 2019)
3.2	Amended and Restated Bylaws of the Registrant and the amendments thereto, as currently in effect (incorporated by reference to Exhibit 3.2 of the Registrant's Current Report on Form 8-K (File No. 001-38944) filed on March 12, 2021)
4.1	Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed on June 10, 2019)
4.2*	Description of Securities
10.1#	2018 Stock Option and Grant Plan, as amended, and form of award agreements thereunder (incorporated by reference to Exhibit 10.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-231747) filed on May 24, 2019)
10.2#	2019 Stock Option and Grant Plan, and form of award agreements thereunder. (incorporated by reference to Exhibit 10.2 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed on June 10, 2019)
10.3#	2019 Employee Stock Purchase Plan. (incorporated by reference to Exhibit 10.3 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed on June 10, 2019)
10.4#	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.4 of the Registrant's Registration Statement on Form S-1 (File No. 333-231747) filed on May 24, 2019)
10.5#	2019 Senior Executive Cash Bonus Plan (incorporated by reference to Exhibit 10.5 of the Registrant's Registration Statement on Form S-1 (File No. 333-231747) filed on May 24, 2019)
10.6#	Form of Amended and Restated Employment Agreement for Executive Officers (incorporated by reference to Exhibit 10.8 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed June 10, 2019)
10.7#	Amended and Restated Employment Agreement for Andrew Cheng (incorporated by reference to Exhibit 10.9 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed June 10, 2019)
10.8#	Amended and Restated Employment Agreement for William White (incorporated by reference to Exhibit 10.10 of the Registrant's Registration Statement on Form S-1/A (File No. 333-231747) filed on June 10, 2019)
10.9**	Exclusive License Agreement, by and between the Registrant and Amgen Inc., dated June 7, 2018 (incorporated by reference to Exhibit 10.9 of the Registrant's Registration Statement on Form S-1 (File No. 333-231747) filed on May 24, 2019)
10.10#	Amended and Restated Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.10 of the Registrant's Annual Report on Form 10-K (File No. 001-38944) filed on February 25, 2022).

Exhibit Number	Exhibit Description
10.11	Office Lease between Gateway Center LP and the Registrant, dated as of February 14, 2020 (incorporated by reference to Exhibit 10.12 of the Registrant's Annual Report on Form 10-K (File No. 001-38944) filed on March 16, 2020)
10.12**	Loan and Security Agreement dated as of June 15, 2022 by and between the Registrant and Hercules Capital, Inc. (Incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-38944 filed on August 5, 2022).
10.13	Warrant, dated June 15, 2022 by and between the Registrant and Hercules Private Global Venture Growth Fund I L.P. (Incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-38944 filed on August 5, 2022).
10.14	Warrant, dated June 15, 2022 by and between the Registrant and Hercules Capital, Inc. (Incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-38944 filed on August 5, 2022).
21.1	List of Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 of the Registrant's Annual Report on Form 10-K (File No. 001-38944) filed on February 25, 2022)
23.1*	Consent of Deloitte & Touche LLP, independent registered public accounting firm
24.1*	Power of Attorney (included on the signatures pages hereto)
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 amended
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 amended
32.1+	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS*	Inline XBRL Instance Document
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 (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.*)

Indicates a management contract or any compensatory plan, contract or arrangement.
* Filed herewith.
** Portions of this exhibit (indicated by asterisks) have been omitted pursuant to Item 601(b)(10) of Regulation S-K.
+ The certifications furnished in Exhibit 32.1 hereto are deemed to be furnished with this Annual Report on Form 10-K and will not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

AKERO THERAPEUTICS, INC.

Date: March 17, 2023

By: /s/ ANDREW CHENG
Andrew Cheng, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Andrew Cheng, Jonathan Young, and William White, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this annual report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed by the following persons in the capacities indicated below and on the dates indicated:

Signature	Title	Date
/s/ ANDREW CHENG Andrew Cheng, M.D., Ph.D.	Chief Executive Officer, President and Director (Principal Executive Officer)	March 17, 2023
/s/ WILLIAM WHITE William White	Executive Vice President, Chief Financial Officer and Head of Corporate Development (Principal Financial and Accounting Officer)	March 17, 2023
/s/ JUDY CHOU Judy Chou, Ph.D.	Director	March 17, 2023
/s/ SETH L. HARRISON Seth L. Harrison, M.D.	Director	March 17, 2023
/s/ JANE P. HENDERSON Jane P. Henderson	Director	March 17, 2023
/s/ TOM HEYMAN Tom Heyman	Director	March 17, 2023
/s/ MARK IWICKI Mark Iwicki	Director	March 17, 2023
/s/ GRAHAM WALMSLEY Graham Walmsley, M.D., Ph.D	Director	March 17, 2023
/s/YUAN XU Yuan Xu, Ph.D	Director	March 17, 2023

EXHIBIT 4.2

Description of the Registrant's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934, as amended

The summary of the general terms and provisions of the registered securities of Akero Therapeutics, Inc.("Akero," "we," or "our") set forth below does not purport to be complete and is subject to and qualified in its entirety by reference to our Fourth Amended and Restated Certificate of Incorporation (our "certificate of incorporation") and our Second Amended and Restated By-laws (our "by-laws" and, together with our certificate of incorporation, our "Charter Documents"), each of which is incorporated by reference as an exhibit to our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission. We encourage you to read our Charter Documents and the applicable provisions of the General Corporation Law of the State of Delaware (the "DGCL") for additional information.

General

Our authorized capital stock consists of One Hundred Fifty Million (150,000,000) shares of common stock, par value $0.0001 per share and Ten Million (10,000,000) shares of undesignated preferred stock, par value $0.0001 per share.

Common stock

The holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of our common stock do not have any cumulative voting rights. Holders of our common stock are entitled to receive ratably any dividends declared by our board of directors out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding convertible preferred stock. Our common stock has no preemptive rights, conversion rights or other subscription rights or redemption or sinking fund provisions.

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding convertible preferred stock.

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "AKRO."

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Preferred stock

Our board of directors will have the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon our liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our company or other corporate action. No shares of convertible preferred stock are outstanding, and we have no present plan to issue any shares of convertible preferred stock.

Anti-Takeover effects of our certificate of incorporation and bylaws and Delaware law

Our certificate of incorporation and bylaws include a number of provisions that may have the effect of delaying, deferring or preventing another party from acquiring control of us and encouraging persons considering unsolicited

tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board composition and filling vacancies

Our certificate of incorporation provides for the division of our board of directors into three classes serving staggered three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of two-thirds or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum. The classification of directors, together with the limitations on removal of directors and treatment of vacancies, has the effect of making it more difficult for stockholders to change the composition of our board of directors.

No written consent of stockholders

Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our bylaws or removal of directors by our stockholders without holding a meeting of stockholders.

Meetings of stockholders

Our certificate of incorporation and bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance notice requirements

Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. Our bylaws specify the requirements as to form and content of all stockholders' notices. These requirements may preclude stockholders from bringing matters before the stockholders at an annual or special meeting.

Amendment to certificate of incorporation and bylaws

Any amendment of our certificate of incorporation must first be approved by a majority of our board of directors, and if required by law or our certificate of incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, board composition, limitation of liability and certificate of incorporation must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class. Our bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the bylaws; and may also be amended by the affirmative vote of a majority of the outstanding shares entitled to vote on the amendment.

Undesignated preferred stock

Our certificate of incorporation provides for 10,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of forum

Our bylaws provide that, unless we consent in writing to the selection of an alternative form, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claims for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of, or a claim based on, a breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim arising out of or pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws (including the interpretation, validity or enforceability thereof); and (4) any action asserting a claim governed by the internal affairs doctrine. Unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act of 1933, as amended. Our bylaws also provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our bylaws is inapplicable or unenforceable if it is challenged in a proceeding or otherwise. Additionally, the forum selection clause in our amended and restated bylaws may limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

Section 203 of the Delaware general corporation law

Upon completion of this offering, we will be subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or
- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, lease, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; and
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statement Nos. 333-232234, 333-237220, 333-254454, and 333-263194 on Form S-8 and No. 333-256229 on Form S-3ASR of our report dated March 17, 2023 relating to the financial statements of Akero Therapeutics, Inc. appearing in this Annual Report on Form 10-K for the year ended December 31, 2022.

/s/ Deloitte & Touche LLP

Morristown, NJ
March 17, 2023

EXHIBIT 31.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO EXCHANGE ACT RULES 13a-14(a) AND 15d-14(a),
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Andrew Cheng, certify that:

1. I have reviewed this Annual Report on Form 10-K of Akero Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 17, 2023

/s/ ANDREW CHENG

Andrew Cheng, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION OF CHIEF 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

I, William White, certify that:

1. I have reviewed this Annual Report on Form 10-K of Akero Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 17, 2023

/s/ WILLIAM WHITE

William White
Executive Vice President, Chief Financial Officer and Head of Corporate Development
(Principal Financial and Accounting Officer)

EXHIBIT 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER AND CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C. SECTION 1350
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

I, Andrew Cheng, certify pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that the annual Report on Form 10-K of Akero Therapeutics, Inc. for the year ended December 31, 2022, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act and that the information contained in such Annual Report on Form 10-K fairly presents, in all material respects, the financial condition and result of operations of Akero Therapeutics, Inc.

Dated: March 17, 2023

/s/ ANDREW CHENG
Andrew Cheng, M.D., Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

I, William White, certify pursuant to Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that the Annual Report on Form 10-K of Akero Therapeutics, Inc. for the year ended December 31, 2022, fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act and that the information contained in such Annual Report on Form 10-K fairly presents, in all material respects, the financial condition and result of operations of Akero Therapeutics, Inc.

Dated: March 17, 2023

/s/ WILLIAM WHITE
William White
Executive Vice President, Chief Financial Officer and Head of Corporate Development
(Principal Financial and Accounting Officer)