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 001-38210

Krystal Biotech, Inc.

(Exact name of Registrant as specified in its Charter)

Delaware	**82-1080209**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
2100 Wharton Street Suite 701 Pittsburgh Pennsylvania	**15203**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (412) 586-5830

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	KRYS	NASDAQ Capital Market

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

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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. Yes ☒ No ☐

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 common stock held by non-affiliates of the Registrant, based on the closing sales price for such stock on June 30, 2022 as reported by The Nasdaq Stock Market, was $1.4 billion.

The number of shares of Registrant's common stock outstanding as of February 20, 2023 was 25,763,743.

Portions of the Registrant's definitive proxy statement relating to its 2023 Annual Meeting of Stockholders are incorporated by reference into Part III of this Report where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Forward-looking statements include all statements that are not historical facts and can be identified by terms such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict", "project," "seek," "should," "target," "will," "would," or similar expressions and the negatives of those terms. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements.

Forward-looking statements appearing in a number of places throughout this Annual Report on Form 10-K include, but are not limited to, statements about the following, among other things:

- the initiation, timing, progress and results of preclinical and clinical trials for Beremagene Geperpavec ("B-VEC", previously "KB103" and now known as Vyjuvek™), KB105, KB104, KB301, KB407, KB408 and any other product candidates, 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;
- the impact of public health crises including the COVID-19 pandemic and measures to contain or prevent these outbreaks may have on our business operations, access to capital, research and development activities, and preclinical and clinical trials for our product candidates;
- the timing, scope or results of regulatory filings and approvals, including timing of final U.S. Food and Drug Administration ("FDA"), marketing and other regulatory approval of our product candidates;
- our ability to achieve certain accelerated or orphan drug designations from the FDA;
- our estimates regarding the potential market opportunity for any of our product candidates;
- our research and development programs for our product candidates;
- our plans and ability to successfully develop and commercialize our product candidates;
- our ability to identify and develop new product candidates;
- our ability to identify, recruit and retain key personnel;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scalability and commercial viability of our proprietary manufacturing methods and processes;
- the rate and degree of market acceptance and clinical utility of our product candidates and gene therapy, in general;
- our competitive position;
- our intellectual property position and our ability to protect and enforce our intellectual property;
- our financial performance;
- developments and projections relating to our competitors and our industry;
- our ability to establish and maintain collaborations;
- our estimates regarding expenses, future revenues, capital requirements and needs for or ability to obtain additional financing;
- our ability to successfully resolve any intellectual property or other claims that may be brought against us;
- the impact of laws and regulations; and
- any statements regarding economic conditions, including statements related to the economic fallout from the COVID-19 pandemic and the impact on our business, or performance and any statement of assumptions underlying any of the foregoing.

Forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in

this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Also, forward-looking statements represent our management's beliefs and assumptions only as of the date of this Annual Report. We undertake no obligation to release publicly any revisions to forward-looking statements as a result of subsequent events or developments, except as required by law. You should read this Annual Report completely and with the understanding that our actual future results may be materially different from what we expect.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, even if new information becomes available in the future.

Throughout this Annual Report, unless the context requires otherwise, all references to "Krystal," "the Company," "we," "our," "us" or similar terms refer to Krystal Biotech, Inc., together with its consolidated subsidiaries.

Summary Risk Factors

Our business is subject to a number of risks, including risks that may prevent us from achieving our business objectives or may adversely affect our business, financial condition, results of operations, cash flows and prospects. These summary risks provide an overview of many of the risks we are exposed to in the normal course of our business and are discussed more fully in "Risk Factors" herein. These risks include, but are not limited to, the following:

- We have incurred net losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.
- We may need to raise additional funding in order to receive approval for our product candidates. Such funding may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development efforts or other operations.
- Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitations.
- Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.
- We are substantially dependent on the commercial success of B-VEC.
- The effect of the COVID-19 pandemic or similar public health crises on our operations and the operations of our third-party partners could cause a disruption of the development efforts for our product candidates and adversely impact our business.
- If we are unable to advance our product candidates through clinical trials, obtain regulatory approval and ultimately commercialize our product candidates, or if we experience significant delays in doing so, our business will be materially harmed.
- Our lead candidate, B-VEC, has not received regulatory approval, and if we obtain regulatory approval to commercialize B-VEC the approval may be for a narrower indication than we seek.
- B-VEC is based on a novel technology, which makes it difficult to predict the time and cost of obtaining regulatory approval.
- Our products may cause undesirable side effects or have other properties that could delay or prevent regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.
- We may encounter substantial delays in our clinical trials, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.
- Even if we obtain regulatory approval for a product candidate, our product candidates will remain subject to regulatory oversight. We will continue to incur costs related to regulatory compliance and are subject to risks related to non-compliance with or changes to applicable laws and regulations, which could cause our product candidates to lose approval.

- If we are not successful in discovering, developing and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.
- We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully market or commercialize our product candidates.
- Delays in obtaining regulatory approvals of the process and facilities needed to manufacture our product candidates or disruptions in our manufacturing process may delay or disrupt our product development and commercialization efforts.
- Although we have established our own manufacturing facility for our product candidates, we may need to continue to utilize third parties for the manufacturing of sterile gel that is mixed with our in-house produced vector for the near future. Therefore, we are subject to the risk that these third parties may not perform satisfactorily.
- If we are unable to expand our market development capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any product revenue.
- If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.
- If we are unable to obtain and maintain adequate U.S. and foreign patent protection for our product candidates, and/or our vector platform, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technologies similar or identical to ours, and our ability to successfully commercialize our current product candidates, any future product candidates we may develop, and our platform technologies may be adversely affected.
- Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.
- Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.
- Our Chief Executive Officer and Chairman of the Board of Directors and our founder, President of R&D and director will have the ability to substantially influence all matters submitted to stockholders for approval.

Item 1. Business.

Overview

We are a biotechnology company focused on developing and commercializing genetic medicines for patients with rare diseases. Using our patented platform that is based on engineered HSV-1, we create vectors that efficiently deliver therapeutic transgenes to cells of interest in multiple organ systems. The cell's own machinery then transcribes and translates the encoded effector to treat or prevent disease. We formulate our vectors for non-invasive or minimally invasive routes of administration at a healthcare professional's office or potentially in the patient's home by a healthcare professional. Our goal is to develop easy-to-use medicines to dramatically improve the lives of patients living with rare diseases and chronic conditions. Our innovative technology platform is supported by in-house, commercial scale Current Good Manufacturing Practice ("CGMP") manufacturing capabilities.

Our Redosable Gene Therapy Platform

We believe that certain inherent features of the HSV-1 virus, combined with the modifications we have made to the viral backbone provides our proprietary gene therapy platform with specific advantages over other viral and non-viral vector platforms including the following:

- **Repeat Administration**: One of the major challenges with many viral vector platforms is that the host immune system may recognize them as foreign agents and launch a robust immune response, resulting in toxicity and rapid removal of the virus. Wild-type HSV-1 is known to persist in the body by becoming latent and hiding from the immune system. We have harnessed the natural ability of HSV-1 to evade host-mediated immunogenicity, while removing specific viral elements that exacerbate the host immunity, thus making our viral vector safer for repeat administration as needed to achieve durability of effect. The immune evasive properties of our vector also enable us to treat patients who may have baseline antibodies to HSV-1, ensuring that prior exposure to the wild-type virus will not limit the number of patients who may be amenable to treatment with our product candidates.
- **Non-Integrating Nature**: Upon entry into cells, the HSV-1 vector persists as an episomal unit in the nucleus, meaning it remains physically separate from the host cell chromosome. Certain other viral vectors currently being used in the development of gene therapy treatments, such as the lentiviral and retroviral vectors, integrate into the host cell DNA to achieve gene expression. Integration into the host cell DNA carries the risk of disrupting host genes. In contrast, a non-integrating vector such as our HSV-1 vector does not carry the same risk of disrupting the expression of host cell genes.
- **Payload Capacity**: HSV-1 is a large virus, approximately 150 kilobases, or Kb, of DNA in size. We have made strategic deletions within this genome to remove critical "immediate early", or IE, genes. These IE genes are required for expression of most of the downstream genes that allow the HSV-1 virus to replicate and destroy host cells. Deletion of these IE genes inhibits expression of most of the viral proteins, making the resulting viral vector replication-deficient and non-toxic. These deletions also enable the vector to easily accommodate a payload of 35Kb or greater without any significant impact on yield or titer. In our lead product candidate, B-VEC, we have successfully inserted two functional copies of the complete ~9Kb human *COL7A1* gene. In contrast, packaging capacity for most other vectors being used is at or under ~10Kb, which limits their ability to deliver large transgenes. In addition, we believe the high payload capacity of our viral vector will allow us to insert multiple and/or combinations of genes or effectors that could enable the treatment of non-monogenic conditions.
- **High Transduction Efficiency**: Poor transduction efficiency has remained a major hurdle for direct delivery of most vectors particularly in the epithelia of the skin and lung. HSV-1 has a natural affinity, or tropism, for epithelial cells. Consequently, our vector penetrates and delivers its payload much more efficiently than other vectors, resulting in transduction efficiencies or cell penetration as high as 95% in cell-based studies. The greater payload capacity of our vector and the high transduction efficiencies achieved allow us to deliver a full gene (or genes) directly to any patient's tissues for off-the-shelf, in vivo gene expression without additional manipulation.
- **Direct Delivery**: Our engineered HSV-1 vector allows for noninvasive or minimally invasive local gene delivery. The advantages of direct delivery are that our products can be administered in a doctor's office or potentially the patient's home, requiring no hospitalization or expensive, invasive, and time-consuming procedures or sophisticated medical teams. Taking gene therapy to the patient minimizes patient travel and circumvents upfront logistical burdens typical of other gene therapy approaches.

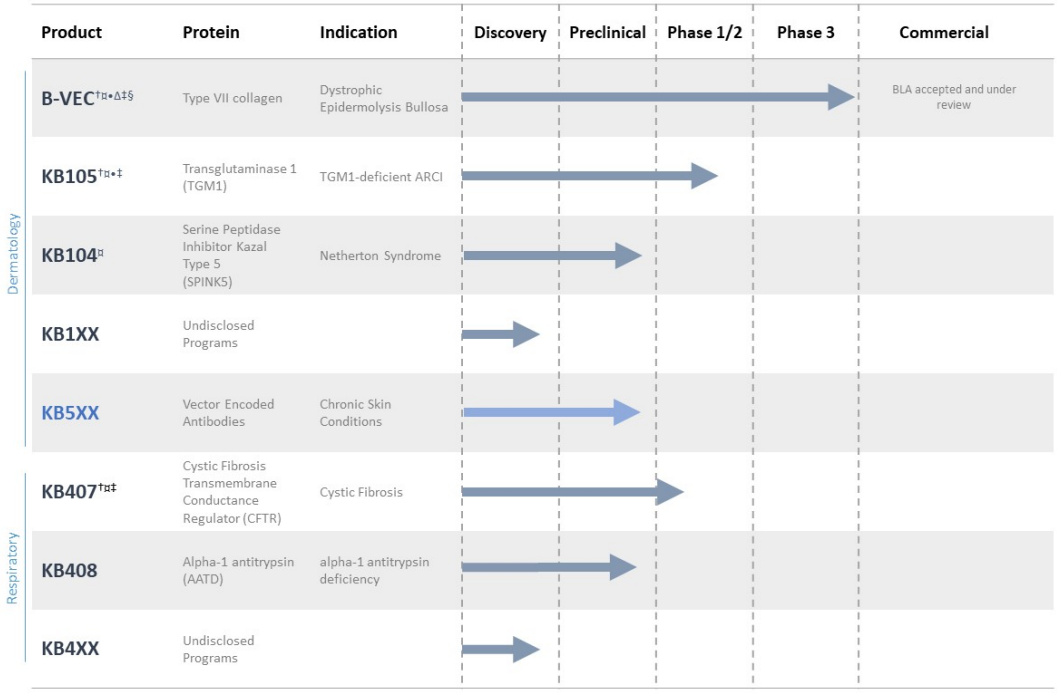
- **Stability**: HSV-1 is extremely stable and resistant to degradation by physical shearing, solvents, and enzymes, facilitating purification and flexibility with final formulation of our product candidates. Our vectors are stable frozen for long-term storage, under refrigerated conditions for short-term storage and shipment, in addition to being stable over several freeze-thaw cycles. This should facilitate our ability to ship our products globally from our manufacturing facilities in Pennsylvania.
- **Reproducible and Scalable Manufacturing**: Successful production of viral vectors involves two steps: (i) the 'upstream' process, which yields a bulk virus harvest; and (ii) the 'downstream' process, which involves purification and concentration of the clinical product. Successful and reproducible execution of both processes is critical for clinical manufacturing and scale-up. Our scientific team collectively has decades of experience and expertise in HSV engineering and purification that has allowed us to successfully optimize our HSV-1 vector production process and develop in-house Chemistry, Manufacturing and Control ("CMC") capabilities.
- **Existing Regulatory Precedent**: The first FDA- and European Medicines Agency ("EMA")-approved oncolytic virus product, Imlygic® by Amgen, for treatment of melanoma, a skin cancer, is based on a genetically engineered HSV-1 virus. Because this product also employs an HSV-1 backbone, it has created a regulatory precedent for approval of an HSV-1-based therapy. In addition, Imlygic® is a chronic therapy, given bi-weekly, which provides support for the use of an HSV-1 backbone in chronic gene therapy of the type we are developing.

The above listed benefits of our innovative platform make it the ideal choice for topical and intradermal applications to treat skin diseases, skin conditions and inhaled formulations to treat respiratory diseases.

Our Product Candidates

The following table summarizes information regarding our product candidates in various stages of clinical and preclinical development as of the date of this Annual Report:

Krystal Biotech Pipeline



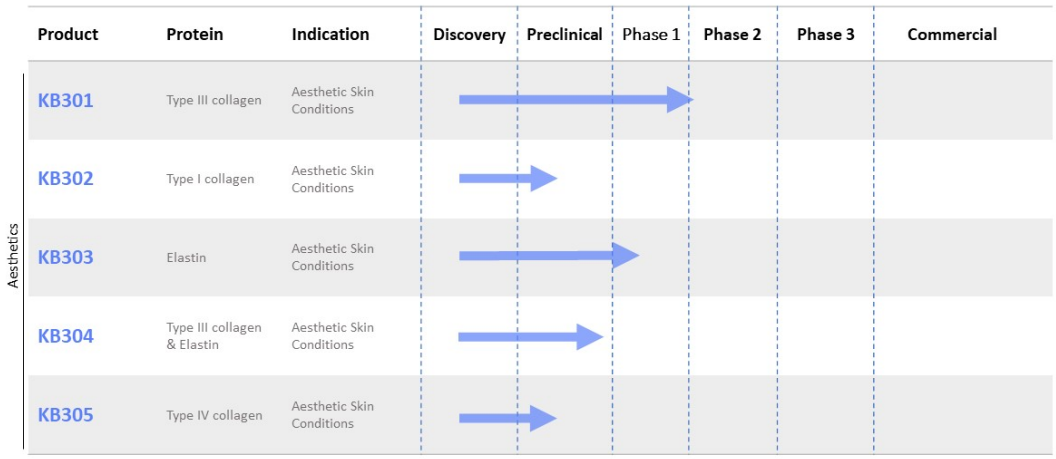
All pipeline compounds are investigational. All pipeline compounds are wholly owned.

†: FDA Orphan Drug Designation;
¤: FDA Rare Pediatric Disease Designation;
•: Fast-track Designation;
Δ: FDA RMAT designation;
‡: EMA Orphan Drug Designation;
§: EMA PRIME Designation.

Rare disease

More prevalent conditions

Jeune Aesthetics Pipeline



All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies. All pipeline compounds are wholly owned.

Dermatology

Investigational Beremagene Geperpavec ("B-VEC") for dystrophic epidermolysis bullosa ("DEB")

Disease Background

DEB is a rare and severe monogenic skin disease. DEB affects the skin and mucosal tissues and is caused by one or more mutations in a gene called *COL7A1*, which is responsible for the formation of the protein type VII collagen ("COL7") that forms anchoring fibrils that bind the dermis (inner layer of the skin) to the epidermis (outer layer of the skin). In DEB patients, the genetic defect in *COL7A1* results in loss or malfunctioning of these anchoring fibrils, leading to extremely fragile skin that blisters and tears from minor friction or trauma. Those who are born with DEB are sometimes called "butterfly children," because their skin is likened to be as fragile as the wings of a butterfly. DEB patients may suffer from open wounds, skin infections, fusion of fingers and toes and gastrointestinal tract problems throughout their lifetime, and may eventually develop squamous cell carcinoma, a potentially fatal condition. We believe that there are, at present, approximately 3,000 diagnosed DEB patients in the United States and approximately 9,000 worldwide. The current standard of care for DEB patients is limited to palliative measures that seek to provide relief from some of the symptoms of DEB but do not meaningfully impact disease outcomes. While not disease-modifying, current treatment is estimated to cost between $200,000 and $400,000 annually per patient in the United States.

B-VEC

B-VEC is a redosable, off-the-shelf gene therapy designed to deliver two copies of the *COL7A1* gene when applied topically, directly onto an open wound. Unlike the current standard of care, B-VEC seeks to treat DEB at the molecular level by providing the patient's skin cells the template to make normal COL7 protein, thereby addressing the fundamental disease-causing mechanism. B-VEC was specifically designed to be easily administered by a healthcare professional in a doctor's office or potentially at the patient's home. The FDA and the European Medicines Agency ("EMA") have each granted B-VEC orphan drug designation for the treatment of DEB, and the FDA has granted B-VEC fast track designation and rare pediatric designation for the treatment of DEB. In addition, the FDA granted Regenerative Medicine Advanced Therapy ("RMAT") to B-VEC for the treatment of DEB and the EMA granted PRIority MEdicines ("PRIME"), eligibility for B-VEC to treat DEB.

We believe our approach to treating DEB is positively differentiated relative to other known efforts to develop corrective treatments that employ autologous approaches. Autologous treatments use a patient's own tissues and cells to manufacture an individualized therapy. Such therapies tend to be expensive, invasive and time consuming to use, and require extensive patient travel, extended hospital stays, highly sophisticated medical teams and procedures.

Clinical Development of B-VEC

We initiated Phase 1 testing of B-VEC in May 2018 at Stanford University, and we announced positive interim results from this clinical study on two patients in October 2018. The Phase 2 portion of the trial commenced in December 2018 at Stanford University, and we announced positive interim results from this clinical study on June 24, 2019. In March 2022, results from the complete Phase 1/2 study of topical B-VEC for the treatment of DEB were published in *Nature Medicine.*

We initiated a pivotal Phase 3 trial ("GEM-3 trial") in July 2020. The GEM-3 trial of B-VEC for the treatment of DEB was a randomized, double-blind, intra-patient placebo-controlled multicenter study designed to evaluate the efficacy and safety of B-VEC for patients suffering from both recessive and dominant forms of DEB. The trial enrolled 31 participants with DEB, aged 6 months or older at time of consent. In each patient, a primary wound pair was identified by the investigator; one wound was randomized to receive a weekly topical application of B-VEC and the other to receive placebo. These primary wounds were treated once weekly for six months until wound closure. If a wound re-opened at any point during the study, weekly dosage resumed until closure. The dose administered to each wound was dependent on the size of the wound. A maximum vector dose per patient per week was defined on the basis of preclinical and clinical safety data. In the event that the maximum dose per patient had not been reached based on dosing of the primary wounds, the study investigators and patients had the opportunity to select additional "secondary" wounds across which the remaining weekly dose was applied. We announced positive results from the GEM-3 trial in November 2021 and in December 2022 full results from the GEM-3 trial were published in the *New England Journal of Medicine.*

In April 2022, following feedback from the FDA, we announced that we planned to offer patients with DEB, who were enrolled in the GEM-3 open label extension study ("OLE"), the opportunity to be dosed in their homes by a health care professional. Further study details are available at www.clinicaltrials.gov under NCT identifier NCT04917887. Nothing included on this website shall be deemed incorporated by reference into this Annual Report on Form 10-K. We are pleased with the on-going progress of the OLE in terms of both patient and physician experiences and plan to provide an update on the OLE study in 2023.

We submitted a Biologics License Application ("BLA") to the FDA for B-VEC for the treatment of DEB in June 2022. The FDA accepted the BLA in August 2022 granting B-VEC a Priority Review Designation with a Prescription Drug User Fee Act ("PDUFA") action date of February 17, 2023. In January 2023, the FDA notified us, that based on manufacturing information submitted to the agency on December 20, 2022 in response to an information request from the FDA, the PDUFA date has been revised to May 19, 2023. In this notification, we were also informed that there will be no Advisory Committee meeting for B-VEC, and that a Risk Evaluation and Mitigation Strategies ("REMS") program was not needed for the B-VEC application.

We submitted a request for Marketing Authorization Application ("MAA") with the European Medicines Agency ("EMA") in November 2022 for B-VEC for the treatment of DEB in patients 6 months and older. The Company was informed by the EMA in January 2023 to modify the PIP waiver request to include patients between birth and 6 months. The Company is modifying the application so that the MAA procedure can officially start in the second half of 2023 with an approval expected in early 2024.

Commercial readiness efforts have been underway for the past two years as we prepare for the potential approval of B-VEC by the FDA and the EMA. In the United States, our Medical Science Liaisons have been interacting with and educating health care professionals ("HCPs") on DEB and the importance of genetic testing in ensuring an accurate diagnosis. We have completed the build of Krystal Connect, our US in-house patient services call center staffed with Krystal employees, and are ready, pending FDA approval of B-VEC, to assist patients, care givers and HCPs interested in accessing B-VEC. Additionally, we have hired, trained and deployed commercial field teams who are interacting with physicians, patients, and commercial payers across the U.S. to educate on DEB and to prepare for a U.S. launch of B-VEC. We are interacting frequently with the leading physicians in the major markets across Europe and in Japan.

KB105 for TGM1-deficient autosomal recessive congenital ichthyosis ("ARCI")

Disease Background

ARCI is a life-long, severe monogenic skin disease. While a number of genetic mutations have been associated with the development of ARCI, the most common cause of ARCI is an inactivating mutation in the human transglutaminase-1 ("*TGM1*") gene encoding the enzyme transglutaminase-1, a protein that is essential for the proper formation of the skin barrier. Mutations in the *TGM1* gene, and the subsequent disruption to the epidermal barrier, leads to pronounced dehydration, trans-epidermal exposure to unwanted toxins and surface microorganisms, and a greatly increased risk of infection. Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life.

Patients suffering from ARCI often exhibit life-long pronounced plate-like scaling of the skin, which is often of a dark color and can cover the whole body. Such patients frequently suffer from exposure of the inner eyelid surface due to turning away of the eyelids from the eye (ectropion), the turning outwards of the lips (eclabium), deformities of joint and nasal cartilage (hypoplasia), scarring alopecia (especially at the edge of the scalp) and a thickening of the skin on the palms of the hands and soles of the feet (palmoplantar keratoderma). Additional complications experienced by ARCI patients include episodes of sepsis, fluid and electrolyte imbalances due to impaired skin barrier function, and failure to thrive, especially during the neonatal period and infancy. Severe heat intolerance and nail dystrophy are also frequently observed. There are currently no treatments targeting molecular correction of this disease. There are approximately 20,000 cases of TGM1-deficient ARCI worldwide and about 400 new cases per year globally.

KB105

KB105 is a redosable, off the-shelf gene therapy designed to deliver two copies of the *TGM1* gene when applied topically, directly to a patient's exfoliated skin. The goal of direct supplementation of TGM1 protein at the site of administration is local correction and phenotypic improvement. Like B-VEC, KB105 was designed to be easily administered by a healthcare professional in the doctor's office or, potentially, at the patient's home.

The FDA and the EMA have each granted KB105 orphan drug designation for the treatment of TGM1-ARCI, and the FDA has granted KB105 fast track designation and rare pediatric designation for the treatment of TGM1-ARCI.

Clinical Development of KB105

In September 2019 we initiated a Phase 1/2 trial in TGM1-ARCI patients. In May 2020, initial clinical data from the Phase 1 portion of the study which enrolled adult patients were presented at the Society for Investigative Dermatology ("SID") meeting. In August 2020, we initiated the second phase of our Phase 2 portion of the clinical trial of KB105 to treat ARCI. We enrolled one patient in whom four rectangular 100cm2 (4-inch x 4-inch) areas of skin were selected as Target Areas (TAs). Each treatment area was assigned to receive repeat doses of 4.0x109 PFU (n=2 treatment areas) or 1.0x1010 PFU (n=2

treatment areas). Each area was dosed on Day 1 and 3, after which dosing continued either every 3 days (n=2 treatment areas) or every 6 days (n=2 treatment areas) up to day 30. Treatment areas were clinically evaluated at pre- and post-KB105 application timepoints, using a 5-point IGA scale (0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = very severe). In July 2021, we announced initial Phase 2 data.

Repeated topical doses of KB105 were well tolerated, and no drug-related adverse effects were reported. No vector shedding or systemic viral exposure was detected at any time point. Improvement on the IGA scale was observed in each treatment area, with the maximum effect observed in TA3 and TA4 that received the highest dose; at day 27, the investigator assigned an IGA score of 2, which was improved as compared to baseline score of 4 in each area. Variable 1-point improvements were observed at other time points and in the treatment areas that received the lowest dose. As in the Phase 1 portion of the trial, TGM1 turnover was observed to be variable but relatively rapid, and the observed IGA improvements were not sustained through day 60.

We plan to resume enrollment in the Phase 2 portion of this trial in the first half of 2023.

KB104 for Netherton Syndrome

Disease Background

Netherton Syndrome is a debilitating monogenic autosomal recessive skin disorder. The disease arises due to mutations in the Serine Protease Inhibitor Kazal-type 5 ("*SPINK5*") gene, resulting in loss of activity of its encoded serine protease inhibitor protein SPINK5 (also known as Lympho-Epithelial Kazal type-related Inhibitor ("LEKTI")). In healthy individuals, SPINK5 is one of the serine protease inhibitors expressed in the outermost layers of the skin, and it plays a critical role in the regulation of serine proteases which hydrolyze extracellular proteins that hold corneocytes together. In patients suffering from Netherton Syndrome, the suppressive effects of SPINK5 on these serine proteases is abolished due to underlying genetic mutations in the *SPINK5* gene. Consequently, hyperactivated serine proteases in the skin cause uncontrolled desquamation, leading to a defective skin barrier.

In infants, severe Netherton Syndrome can be associated with failure to thrive, hypernatremic dehydration secondary to excess fluid loss, delayed growth, short stature, and recurrent infections. Clinically, Netherton Syndrome is characterized by congenital ichthyosiform erythroderma, hair shaft defects, recurrent infections, and a defective skin barrier. A predisposition to allergies, asthma, and eczema is also characteristic of Netherton Syndrome. Ultimately, those afflicted by Netherton Syndrome often experience chronic skin inflammation, severe dehydration, and stunted growth.

There are approximately 38,000 cases of patients worldwide and about 700 new cases per year globally. There are no current approved treatments for Netherton Syndrome. Existing approaches are limited to palliative treatments, including topical moisturizers, repair formulas and steroids.

KB104

KB104 is a redoseable off-the-shelf gene therapy designed to deliver two copies of the *SPINK5* gene to relevant skin cells when applied topically. By directly supplementing the skin with functional SPINK5, the goal of therapy is to locally correct the desquamation and improve the barrier function of the skin. In preclinical testing a properly localized human *SPINK5* gene was detected 48 hours after topical KB104 application in mice without toxicity. KB104-mediated human SPINK5 was expressed in the correct layer of skin at the transcript and protein levels.

The FDA has granted KB104 rare pediatric designation for the treatment of Netherton Syndrome.

We plan to file an investigational new drug ("IND") application with the FDA and initiate a clinical trial of KB104 in Netherton Syndrome in 2023.

Respiratory

KB407 for Cystic Fibrosis ("CF")

Disease Background

CF is the most common inherited genetic disorder in the United States and is caused by mutations in the cystic fibrosis transmembrane conductance regulator ("*CFTR*") gene. Lack of functional CFTR protein in secretory airway epithelia results in defective Cl-, bicarbonate, and thiocyanate secretion, coupled with enhanced Na+ absorption and mucus production, leading to dehydration and acidification of the airway surface liquid. CF is characterized by recurrent chest infections, increased airway secretions, and eventually, respiratory failure. While CF comprises a multiorgan pathology affecting the upper and lower

airways, gastrointestinal and reproductive tracts, and the endocrine system, the primary cause of morbidity and mortality in CF is due to progressive lung destruction.

According to the U.S. Cystic Fibrosis Foundation ("CFF"), the median age at death for patients with CF in the United States was 30.8 years in 2018. Currently approved CFTR modulating therapies are limited to patients with specific genetic mutations and there is a significant unmet medical need for the approximately 10% of patients with CF who have genetic mutations non-amenable to currently approved CFTR small molecule "modulators". According to the CFF, approximately 30,000 patients in the United States and more than 70,000 patients worldwide are living with CF, and approximately 850 new cases of CF were diagnosed in 2018.

KB407

KB407 is a redosable off the-shelf gene therapy designed to deliver two copies of the full-length *CFTR* transgene directly to the airway epithelia via inhaled (nebulized) administration. By inducing expression of full length, normal CFTR protein in the lung, treatment with KB407 has potential to restore ion and water flow into and out of lung cells to correct the lung manifestations of the disease in patients regardless of their underlying genetic mutation. Preclinical efforts to date have shown that KB407 successfully transduces patient-derived epithelial cells and delivers functional CFTR in vitro in 2D and 3D organotypic systems, and is amendable to non-invasive inhaled administration in vivo, as indicated by successful delivery to the lungs through the use of a clinically relevant nebulizer in small animal models. Successful delivery and distribution throughout the lung also was observed in a nonhuman primate.

The FDA and the EMA have each granted KB407 orphan drug designation for the treatment of cystic fibrosis, and the FDA has granted KB407 rare pediatric designation for the treatment of cystic fibrosis.

Clinical Development of KB407

In September 2021, we announced that we were granted approval by the Bellberry Human Research Ethics Committee ("HREC") in Australia to conduct a Phase 1 clinical study of inhaled KB407 in patients with CF. We previously received license to evaluate KB407 from Australia's Office of the Gene Technology Regulator ("OGTR"). We plan to dose our first patient in the Phase 1 clinical trial in Australia in the first half of 2023.

We announced, in August 2022, that the FDA had accepted our IND application to evaluate KB407 in a clinical trial to treat patients with CF. We are closely working with the Therapeutics Development Network ("TDN") of the CFF to validate our clinical protocol and plan on initiating a Phase 1 clinical trial in the U.S. in the first half of 2023.

KB408 for Alpha-1 antitrypsin deficiency ("AATD")

Disease Background

AATD is a genetic condition caused by mutations that lead to decreased levels and/or decreased functionality of the alpha-1- antitrypsin ("AAT") protein. AATD lung disease is a consequence of diminished or absent functional protein in the lungs due to impaired transport into, and low concentrations in, patient plasma. Low AAT serum levels can result in life threatening, progressive pulmonary impairment and severe respiratory insufficiency, manifesting as chronic obstructive pulmonary disease ("COPD") and panacinar emphysema. The lung degeneration observed in AATD patients derives from an unopposed, and therefore enhanced, neutrophil elastase ("NE") activity, leading to an excessive degradation of elastin, collagen, and fibronectin. The absence of proper NE inactivation by functional AAT ultimately results in lung tissue destruction, airway obstruction, and an increased inflammation state that compromises the integrity of the organ and contributes to an inadequate response to insults, including inefficient pulmonary bacterial clearance.

There are an estimated 90,000 to 100,000 people in the U.S. with severe AAT deficiency. Currently, many AATD patients undergo "augmentation therapy" consisting of weekly intravenous ("IV") infusions of either plasma-purified AAT or recombinant AAT. This therapy requires burdensome weekly IV infusions and often includes the risk of exposure to bloodborne pathogens connected with the use of blood-derived products.

KB408

KB408 is an inhaled (nebulized) formulation of our proprietary vector, designed to deliver two copies of the *SERPINA1* transgene that encodes functional, full-length human protein, for the treatment of AATD. Preclinical studies to date have shown that KB408 successfully transduces patient-derived lung epithelial cells in vitro, leading to production and secretion of full-length human AAT protein capable of irreversibly binding its cognate target NE. In small animal models, analysis of lung tissue biopsies, serum, and bronchoalveolar lavage fluid harvested 24 and 48 hours after inhalation of KB408 shows secretion of full-length AAT protein, with no evidence of significant or systemic toxicity.

We are planning to file an IND for KB408 to treat AATD patients in 2023.

Aesthetics

While our focus is on the development of gene therapies to treat serious rare diseases, we are also evaluating the potential of our platform to address more prevalent and/or non-genetic conditions. To that end, in April 2019, we incorporated Jeune Aesthetics, Inc. ("Jeune Aesthetics"), a wholly-owned subsidiary, for the purposes of undertaking preclinical and clinical studies for aesthetic skin conditions.

KB301 for aesthetic skin conditions

Disease Background

The skin is largely composed of collagen-rich connective tissue, with dermal collagen, composed primarily of types 1 and 3 collagen fibrils, representing >90% (dry weight) of human skin. The characteristics of skin aging are largely due to aberrant collagen homeostasis, including reduced collagen biosynthesis, increased collagen fibril fragmentation, and progressive loss of dermal collagen culminating in a net collagen deficiency, resulting from both intrinsic (*e.g.*, passage of time, genetics) and extrinsic (*e.g.*, chronic light exposure, pollution) pressures.

Facial injectables, including hyaluronic acid, botulinum toxin type A, collagen, polymer fillers, and calcium hydroxyapatite microparticles, are intended to correct perceived facial defects (*e.g.*, fine lines, shallow wrinkles, and deeper furrows), and are administered for both cosmetic and therapeutic indications. In 2017, the global facial injectables market generated more than $7.2 billion in revenue from approximately 8.5 million procedures performed, with a majority (~70%) of revenue being generated in the aesthetic setting. While the United States and Europe represent the largest markets for facial injectables to-date, significant expansion in market share is projected for Asia and Latin America in the coming years. Due to the rising awareness of cosmetic procedures, the growing geriatric population, and a shift from invasive to minimally/non-invasive treatment options, the aesthetics facial injectables market is projected to grow to more than a $12 billion industry by 2025.

KB301

KB301 leverages our clinical experience in delivering genes of interest to the skin, and is designed to stimulate biorejuvenation of the skin via delivery of the gene that encodes for type III collagen ("COL3") when administered via intradermal injection. We believe that our approach of directed expression of full-length human type III collagen via intradermal application of KB301 provides a unique and straightforward approach to restoring collagen homeostasis, and by extension, reconstructing an optimal physiologic environment in the skin to treat wrinkles or other presentations of aged or damaged skin.

Clinical development of KB301

We initiated a Phase 1 clinical trial, the PEARL-1 trial, for the treatment of aesthetic skin conditions in August 2020. The Phase 1 dose-ranging trial evaluated the safety, tolerability, and initial efficacy of intradermal injections of KB301 in adult subjects aged 18-75 (NCT04540900). KB301 was well tolerated, and we were able to biopsy and demonstrate proof-of-mechanism. Complete results from Cohort 1 focused on safety were presented at the 2021 SID Annual Meeting.

In March 2022, we announced positive proof-of-concept efficacy and safety data from Cohort 2 of the PEARL-1 study of KB301 for the treatment of aesthetic skin indications. Cohort 2 was a randomized, double-blind, placebo-controlled clinical trial that evaluated the safety and efficacy of KB301 for the improvement of fine lines and skin texture in the lower and upper cheek and for improvement in skin thickness in the knee. Cohort 2 enrolled 27 subjects across two trial sites. Bilateral treatment areas included the neck behind the ear to assess initial safety and on the cheek below and above the zygomatic arch (lower and upper cheek), and around the knee. Subjects were randomized 2:1 to receive low dose KB301 or placebo in the upper cheek and knee as multiple micro depot injections over the selected treatment area with a 33 G needle. Subjects receiving KB301 in the lower check were randomized 2:1 to receive either low dose KB301, high dose KB301 or placebo. Four patients dropped out of the Cohort 2 study – one subject following the initial safety assessment behind the ear, two subjects for unspecified reasons, and one subject due to unevenness in face between active and placebo during the study.

A subset of subjects from the PEARL-1 Cohort 2 trial (Cohort 3) were enrolled into a durability trial to look for duration of effect, reduction of the unevenness in placebo treated sites, and for long term safety monitoring. Ten subjects from the PEARL-1 Cohort 2 study were enrolled in the durability trial, an open-label study to assess duration of effect below the zygomatic arch (the lower cheek area). The extension cohort enrolled subjects who had received the high dose regimen of KB301 during the efficacy cohort in one or both of their lower cheeks. Subject Satisfaction Scores and Investigator Assessments were measured monthly for three consecutive visits that correspond to timepoints up to nine-months following

administration of the last dose of KB301. In addition, subjects with placebo-treated lower cheeks were dosed with KB301 during the open-label extension cohort to normalize their appearance. In November 2022, we announced nine-month durability of effect in Cohort 3 of the PEARL-1 study of KB301.

We are planning to initiate a Phase 2 study in fine lines in 2023.

Future Opportunities

We believe the ability to redose, as well as the large payload capacity of our proprietary vectors, will allow us to deliver multiple genes and other effectors, which could enable development of therapies to treat non-monogenic skin diseases like psoriasis and atopic dermatitis, as well as conditions that are not necessarily the result of an inherited genetic defect, such as chronic wounds. For example, as proof-of concept we have generated a library of vectors designed to deliver anti-inflammatory antibodies. Further, we evaluated one of these vectors in an animal model of atopic dermatitis where expression of the vector-encoded-antibody was confirmed and efficacy was observed.

If we are able to successfully generate product candidates to treat these non-orphan diseases, we intend to seek collaborative alliances towards the development and potential commercialization of these therapies.

Manufacturing

In-House CGMP Facilities

We have built in-house CGMP facilities to enable better quality control, shorten lead times, lower costs and strengthen command over our intellectual property. Our first facility, ANCORIS, a commercial scale CGMP-compliant manufacturing facility, is producing the long-term extension study material for B-VEC at commercial scale, and we expect to produce initial commercial launch material of B-VEC at the facility following FDA approval. In December 2022, the FDA completed a successful audit of our ANCORIS facility as part of the B-VEC BLA review process.

Our second commercial scale CGMP facility, ASTRA, is expected to be completed and validated in 2023. It is a state-of-the-art CGMP manufacturing facility that, in addition to adding significant capacity to support the growing pipeline, will also allow the in-house incorporation of raw material preparation, excipient manufacturing, testing, packaging, labeling and distribution, thereby fully integrating all components of the supply chain from starting materials to patient experience. We announced the ground breaking of ASTRA in January 2020. We are planning to initiate our first GMP run in ASTRA in 1H 2023.

Our proprietary manufacturing process which was initially developed for B-VEC and is now being used across our platform, was developed and optimized internally and involves both an upstream production process and downstream purification process. Recombinant viral vectors are rendered incapable of, or attenuated for, replacing in human cells by removal of specific viral machinery, including packaging proteins. However, to produce the recombinant virus, these viral proteins have to be re-introduced into the virus production process so that the viral vector can be packaged. In most other viral vector production systems, the missing viral proteins are supplied in one or more individual helper plasmids, along with the base viral vector plasmid. All the plasmids are then co-transfected into a production cell line in the presence of a transfection agent to facilitate viral vector production and packaging. The difficulty of this approach is that it requires c-scale manufacturing and qualification of each of the packaging plasmids and optimization of the transfection method. Even with optimized reagents and methods, significant batch-to-batch variability is seen in viral vector yield and titer that, we believe, drives up the cost of viral vector manufacturing and scale-up and increases the risk of failure during manufacturing.

Our proprietary upstream process for HSV-1 production avoids the aforementioned issues. Our process requires three critical components:

- Production of a master virus seed stock (“MVSS”);
- Production of complementing master cell bank (“MCB”); and
- Optimized transduction parameters.

For each of our product candidates, we generate a MVSS which is scaled up from a single purified clone of the modified HSV-1 vector expressing the therapeutic effector. The MCB is a complementing cell line that stably expresses the HSV-1 viral proteins that are required for HSV-1 growth but have been deleted from the recombinant HSV-1 backbone. By introducing the deleted proteins into the MCB, as opposed to including them in the viral replication process via co-transfection of individual plasmids, we eliminate the need for multiple qualifications of the plasmids or variability in transfection efficiency from batch to batch, that other production processes face. Infection of the MCB with the MVSS at the optimal concentration results in production of the viral particle. Once the MCB, the MVSS, and the conditions of infection are established, virus

production and resultant yield and titer are highly reproducible and scalable over multiple runs, and the risk of failure is minimal.

Optimization of MCB, MVSS and production methods requires extensive knowledge and technical experience with the HSV-1 genome and significant upfront effort to design and select the best virus seed stock and complementing cell line. To date we have screened hundreds of cell line clones to find the best complementing cell lines, and similarly designed and generated the optimal virus seed stocks for each of our product candidates. The viral seed stock expresses the therapeutic proteins under the control of strong constitutive or tissue-specific promoters and additional non-coding regulatory sequences have been included to optimize gene expression. We also have optimized the transduction conditions to reproducibly obtain high yields of the virus.

Unlike the upstream process, steps used to purify and concentrate the viral vector product are often common across different viral vector platforms and usually involve multiple stages of purification, clarification, concentration, and diafiltration, with the ultimate goal to remove contaminants and concentrate the product. We have developed a robust and reproducible process for purifying our viral vector to required concentrations for clinical use, while successfully removing contaminants to meet FDA guidelines.

We believe that the MVSS and MCB are a vital part of the production of our product candidates, as they ensure the reproducible production of multiple clinical and potentially commercial batches in a short six-week cycle time frame and in a cost-effective manner.

We have made significant investments in developing the most comprehensive and optimized manufacturing process for our vector product candidates including:

- A proprietary vector manufacturing technique and a series of high-efficiency purification processes that produce highly purified therapeutic vectors and can be adapted for each product candidate; and
- A critical list of CGMP assays to accurately characterize our process and the HSV-1 vectors we produce.

Competition

The biotechnology and pharmaceutical industries are highly competitive. In particular, the field of gene therapy is characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. Some of our competitors have substantially greater financial resources and larger research and development organizations. In addition, our experience in clinical trials, obtaining FDA and other regulatory approvals, and manufacturing and commercialization of products may be more limited.

Epidermolysis Bullosa

A number of companies are developing drug candidates for EB. There is no approved treatment for DEB at this time. We believe our competitors fall into two broad categories:

- **Corrective approaches:** We are aware of two companies, Abeona and Castle Creek Pharmaceuticals, which are developing autologous or grafting gene therapy approaches to treating DEB. We are also aware of a recombinant-protein based approach being developed by Phoenix Tissue Repair.
- **Palliative Treatments:** We are aware of companies, such as Amryt Pharmaceuticals and Castle Creek Pharmaceuticals, which are developing product candidates taking a palliative approach to treating the disease.

Autosomal Recessive Congenital Ichthyosis

We are aware of companies such as Novartis Inc. and Patagonia Pharmaceuticals, LLC who have conducted clinical trials for ARCI in the past. We are unaware of any companies conducting active clinical trials in ARCI presently.

Netherton Syndrome

We are aware that Novartis Inc. has conducted clinical trials for Netherton Syndrome. We are unaware of any companies currently conducting active clinical trials in Netherton Syndrome presently.

Cystic Fibrosis

We are aware of several preclinical or early clinical stage nucleic-acid-based programs for the treatment of CF including TranslateBio, ReCode Therapeutics, Spirovant, and 4D Molecular Therapeutics.

Intellectual Property

Our success depends in part on our ability to maintain proprietary protection surrounding our product candidates, platform technology, and know-how, to operate without infringing the proprietary rights of others, and to prevent others from infringing our proprietary rights. We have a portfolio of patents, patent applications and other intellectual property owned entirely by the Company that protect our core platform technology and products based thereupon, and affords us freedom to use this platform for the development of novel therapeutics for multiple applications. We continue to advance our intellectual property portfolio actively through the filing of new patent applications, divisionals, and continuations relating to our technologies as we deem appropriate.

In addition to our patents, we rely on trade secrets and know-how to develop and maintain our competitive position. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and intellectual property assignment agreements with our employees, consultants and commercial partners. We also seek to preserve the integrity and confidentiality of our data, trade secrets, and know-how, including by implementing measures intended to maintain the physical and electronic security of our research and manufacturing facilities, as well as our information technology systems.

Platform

Patent Number	Country / Region*	Patent Type	Expiration Date**	Owner / Licensor
U.S. 10,441,614	United States	**Composition of Matter & Methods of Use** – The Skin TARgeted Delivery platform, or STAR-D, for skin-targeted therapeutics, as well as methods of its use for delivering any effector of interest to the skin	12/28/2036	Krystal
U.S. 11,185,564	United States	**Methods of Use** – Methods of their using replication-defective HSV vectors for delivering any effector as skin-target therapeutics interest to the skin.	12/28/2036	Krystal

B-VEC (Beremagene Geperpavec)

Patent Number	Country / Region*	Patent Type	Expiration Date**	Owner / Licensor
U.S. 9,877,990	United States	**Composition of Matter & Methods of Use** – Compositions comprising HSV vectors encoding certain effectors, including the effector encoded in B-VEC, and methods of using the same for providing prophylactic, palliative or therapeutic relief of a wound, disorder or disease of the skin	12/28/2036	Krystal
U.S. 10,155,016	United States	**Composition of Matter** – Covers compositions containing B-VEC, formulated for alternate routes of administration	12/28/2036	Krystal
EP 3 377 637 B1	Europe	**Composition of Matter** – Pharmaceutical compositions comprising B-VEC, as well as uses thereof, including for providing prophylactic, palliative or therapeutic relief of a wound, disorder or disease of the skin.	12/28/2036	Krystal

KB105

Patent Number	Country / Region*	Patent Type	Expiration Date**	Owner / Licensor
U.S. 10,525,090	United States	**Composition of Matter & Methods of Use** – KB105, as well as medical applications of this product for treating TGM1-deficient ARC	4/11/2039	Krystal

KB301

Patent Number	Country / Region*	Patent Type	Expiration Date**	Owner / Licensor
U.S. 10,786,438	United States	**Composition of Matter & Methods of Use** – Pharmaceutical compositions comprising HSV vectors encoding one or more cosmetic proteins, as well as methods of their use for improving skin condition, quality, and/or appearance.	4/26/2039	Krystal

KB407

Patent Number	Country / Region*	Patent Type	Expiration Date**	Owner / Licensor
U.S. 10,829,529	United States	**Methods of Use –** Methods of using KB407 for the treatment of cystic fibrosis and other diseases causing progressive lung destruction	2/07/2040	Krystal

* Granted patents in the U.S. and Europe ("EP") are shown. Additional patent protection in the U.S. and Europe or other countries or regions through pending or granted counterparts may be available.

** Stated expiration dates do not account for any patent term extension, supplemental protection certificate, or pediatric extensions that may be available.

Government Regulation and Product Approval

In the United States, the FDA regulates biologic products including gene therapy products under the Federal Food, Drug, and Cosmetic Act ("FDCA"), the Public Health Service Act ("PHSA"), and regulations and guidance implementing these laws. The FDCA, PHSA and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, importation, advertising and other promotional practices involving biologic products. IND applications to the FDA are required before conducting human clinical testing of biologic products. Additionally, each clinical trial protocol for a gene therapy product candidate is reviewed by the FDA, and in limited instances the National Institutes of Health ("NIH"), through its Recombinant DNA Advisory Committee, or RAC. The FDA's authorization also must be obtained before marketing of biologic products. The process of obtaining regulatory approvals or licenses and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals to successfully develop and commercialize our product candidates.

Within the FDA, the Center for Biologics Evaluation and Research ("CBER") regulates gene therapy products. Within CBER, the review of gene therapy and related products is in the Office of Therapeutic Products ("OTP") and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee ("CTGTAC") to advise CBER on its reviews. CBER works closely with the NIH and the RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA has provided guidance for the development of gene therapy products generally, including a growing body of guidance documents on CMC clinical investigations and other areas of gene therapy development, all of which are intended to facilitate the industry's development of gene therapy products.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biologic Products Development Process

The FDA must authorize the marketing of a product candidate for marketing in the United States. The process required by the FDA before a biologic product candidate may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and in vivo studies in accordance with the FDA's current Good Laboratory Practice ("GLP"), regulations and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an IND application, which allows human clinical trials to begin unless FDA objects within 30 days;
- approval by each clinical trial site's Institutional Review Board ("IRB") and Institutional Biosafety Committee ("IBC"), before the clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's Good Clinical Practice ("GCP") regulations and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biologic product candidate for its intended use;
- preparation and submission to the FDA of an application for marketing approval that includes substantial evidence of safety, purity and potency from results of nonclinical testing and clinical trials;
- review of the product by an FDA advisory committee, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biologic product candidate is produced to assess compliance with CGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the biologic product candidate's identity, safety, strength, quality, potency and purity;
- potential FDA audit of the nonclinical and clinical trial sites that generated the data in support of the application; and
- payment of user fees and FDA review and marketing authorization..

Before testing any new biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as in vivo studies to assess the potential safety and activity of the product candidate and to establish a rationale for therapeutic use. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Concurrent with clinical trials, companies usually must complete some long-term preclinical testing, such as animal studies of reproductive adverse events and carcinogenicity and must also develop additional information about the chemistry and physical characteristics of the biological product and finalize a process for manufacturing the biological product in commercial quantities in accordance with CGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the biological product candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final biological product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted, to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its

IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA also may impose clinical holds on a biologic product candidate at any time before or during clinical trials due to safety concerns or non-compliance. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND for our future product candidates will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Human Clinical Trials Under an IND

Clinical trials involve the administration of the biologic product candidate to healthy volunteers or patients under the supervision of qualified investigators who generally are physicians not employed by or under the control of the trial sponsor. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. An IND becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial must be reviewed and approved by an IRB and IBC at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers items such as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject, or their legal representative, reviews and approves the study protocol, and must monitor the clinical trial until completed. Clinical trials involving recombinant DNA also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research that utilizes recombinant DNA at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

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

- Phase 1. The biologic product candidate initially is introduced into a small number of healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early understanding of its effectiveness. In the case of some product candidates for severe or life-threatening diseases, especially when the product candidate may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients. Phase 1 clinical trials of gene therapies are typically conducted in patients rather than healthy volunteers.
- Phase 2. The biologic product candidate is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product candidate for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- Phase 3. Phase 3 clinical trials are commonly referred to as "pivotal" studies, which typically denotes studies that present the data the FDA or other relevant regulatory agencies will use to determine whether or not to approve a biologic product. In Phase 3 studies, the biologic product candidate is administered to an expanded patient population, generally at multiple geographically dispersed clinical trial sites in adequate and well-controlled clinical trials to generate sufficient data to statistically confirm the potency and safety of the product for approval. These clinical trials are intended to establish the overall risk/benefit ratio of the product candidate and provide an adequate basis for product labeling.
- Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

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.

Additional Regulation for Gene Therapy Clinical Trials

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving the use of gene therapy. The FDA has issued various guidance documents regarding gene therapies, which outline additional factors the FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the CMC information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire. The NIH and the FDA have a publicly accessible database, the Genetic Modification Clinical Research Information System, which includes information on gene therapy trials and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these trials.

U.S. Review and Approval Processes

The results of the preclinical tests and clinical trials, together with detailed information relating to the product's CMC and proposed labeling, among other things, are submitted to the FDA as part of a BLA or other submission requesting authorization to market the product for one or more indications. For gene therapies, selecting patients with applicable genetic defects is a necessary condition to effective treatment. For the therapy we are currently developing, we believe that diagnoses based on existing genetic tests developed and administered by laboratories certified under the Clinical Laboratory Improvement Amendments ("CLIA") are sufficient to select appropriate patients and will be permitted by the FDA. Under the PDUFA, each BLA (or New Drug Application ("NDA") for some biologics) must be accompanied by a significant user fee. The FDA adjusts the PDUFA user fees on an annual basis. The PDUFA also imposes an annual product fee for biologics and an annual establishment license fee on facilities used to manufacture prescription biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs or NDAs for product candidates designated as orphan drugs, unless the product candidate also includes a non-orphan indication.

The FDA reviews a BLA within 60 days of submission to determine if it is substantially complete before it 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 that 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. Once the submission is accepted for filing, the FDA begins an in-depth, substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product candidate is safe and potent, or effective, for its intended use, has an acceptable purity profile and whether the product candidate is being manufactured in accordance with CGMP to assure and preserve the product candidate's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the product approval process, the FDA also will determine whether a REMS program is necessary to assure the safe use of the product candidate.

REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. A REMS could include medication guides, physician communication plans and elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will inspect the facilities at which the product candidate is manufactured. The FDA will not approve the product candidate unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product candidate within required specifications. Additionally, before approving a BLA, the FDA typically will inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND trial requirements and GCP requirements.

On the basis of the BLA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter or license authorizes commercial marketing of the biologic product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or

information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the BLA, the FDA will issue an approval letter.

If a product candidate receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post-marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biologic product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

The FDA has agreed to specified performance goals in the review of BLAs under the PDUFA. One such goal is to review standard BLAs in 10 months after the FDA accepts the BLA for filing, and priority BLAs in six months, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change from time to time. 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.

Fast Track Designation

Fast Track designation is granted to drugs being developed for the treatment of serious or life-threatening diseases or conditions where there is an unmet medical need. The purpose of the Fast Track designation provision is to help facilitate development and expedite the review and potential approval of drugs to treat serious and life-threatening conditions. Sponsors of drugs that receive Fast Track designation have the opportunity for more frequent interactions with the FDA review team throughout the development program. These can include meetings to discuss study design, data required to support approval, or other aspects of the clinical program. Additionally, products that have been granted Fast Track designation may be eligible for priority review of a BLA application and the FDA may consider reviewing portions of the submission before the sponsor submits the complete application, also known as a rolling review.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may designate a biologic product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a biologic product available in the United States for treatment of the disease or condition will be recovered from sales of the product.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, meaning that the FDA may not approve any other applications to market the same drug or biologic product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or if the party holding the exclusivity fails to assure the availability of sufficient quantities of the drug to meet the needs of patients with the disease or condition for which the drug was designated. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Other benefits include reduced regulatory fees, protocol assistance and tax credits for certain clinical research costs.

Orphan medicinal product status in the European Union ("EU") has similar, but not identical benefits.

Regenerative Medicine Advanced Therapy Designation

Established under the 21st Century Cures Act, RMAT designation is a program designed to expedite the development and approval of regenerative medicine products, including gene therapy products. An investigational therapy is eligible for the RMAT designation if it is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition, and preliminary clinical evidence indicates a potential to address unmet medical needs for that disease or condition. The designation includes all the benefits of the FDA's Fast Track and Breakthrough Therapy designations and enables the ability to work more closely and frequently with the FDA to discuss surrogate or intermediate endpoints to support the potential acceleration of approval and satisfy post-approval requirements.

Prime Designation

The PRIME designation is awarded by the EMA to promising medicines that target an unmet medical need. These medicines are considered priority medicines by the EMA. To be eligible and accepted for PRIME, a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data coupled with non-clinical data. Through PRIME, the EMA offers enhanced support to medicine developers including early interaction and dialogue, and a pathway for

accelerated evaluation by the agency. The program is intended to optimize development plans and expedite the review and approval process so that these medicines may reach patients as early as possible.

Rare Pediatric Disease Priority Review Voucher

The FDA also offers a rare pediatric disease drug designation. If a drug receives the designation of a "rare pediatric disease" drug, it is eligible during the FDA marketing process to apply for a Rare Pediatric Disease Priority Review Voucher. According to the FDA website, under the Rare Pediatric Priority Review Voucher Program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of product candidates, some of a sponsor's U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and 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 generally is one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biologic product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. Moreover, a given patent may only be extended once based on a single product. The United States Patent and Trademark Office ("USPTO"), in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Post-Approval Requirements

Rigorous and extensive FDA regulation of biologic products continues after approval, particularly with respect to CGMP requirements. Manufacturers are required to comply with applicable requirements in the CGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biologic products include reporting of CGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product; recordkeeping requirements; reporting of adverse effects; reporting updated safety and efficacy information; and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA, together with a release protocol, showing a summary of the history of manufacture of the lot and the results of all tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products before releasing the lots for distribution. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency and effectiveness of biologic products. A sponsor also must comply with the FDA's advertising and promotion requirements, such as the prohibition on promoting products for uses or in- patient populations that are not described in the product's approved labeling (known as "off-label promotion").

Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

Government Regulation Outside of the United States

In addition to regulations in the United States, sponsors are subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of biologic products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not a sponsor obtains FDA approval for a product, a sponsor 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 request for a Clinical Trial Authorization ("CTA") must be submitted to the competent regulatory authorities and the competent Ethics Committees in the EU Member States in which the clinical trial takes place, much like FDA and the IRB, respectively. Once the CTA request is approved in accordance with the EU and the EU Member State's requirements, clinical trial development may proceed. The requirements and processes governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCPs and the applicable

regulatory requirements of the country or countries in which the clinical trial is performed, as well as the ethical principles that have their origin in the Declaration of Helsinki (whichever provides the greater protection to the clinical trial participants).

Failure to comply with applicable foreign regulatory requirements may result in, among other things, fines; suspension, variation or withdrawal of regulatory approvals; product recalls; seizure of products; operating restrictions; and criminal prosecution.

Other Healthcare Laws and Regulations

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and use of pharmaceutical products that are granted marketing approval. Arrangements with third-party payors, existing or potential customers and referral sources are subject to broadly applicable fraud and abuse and other healthcare laws and regulations, and these laws and regulations may constrain the business or financial arrangements and relationships through which manufacturers market, sell and distribute the products for which they obtain marketing approval. Such restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or kind, in exchange for, or to induce, either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers, on the one hand, and prescribers, purchasers and formulary managers on the other. The Patient Protection and Affordable Care Act ("PPACA") amended the intent requirement of the federal Anti-Kickback Statute. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to commit a violation;
- the federal false claims and civil monetary penalties laws, including the civil False Claims Act ("FCA"), which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid or other third-party payors that are false or fraudulent, or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government. Certain marketing practices, including off-label promotion, also may implicate the FCA. In addition, the PPACA codified case law 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 FCA;
- the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services ("CMS") information related to payments and other transfers of value to physicians, certain other healthcare providers and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;
- the federal Health Care Fraud statute imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as amended by the Health Information Technology for Economic and Clinical Health Act, and its implementing regulations, which imposes obligations, including mandatory contractual terms, with respect to safeguarding the transmission, security and privacy of protected health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for federally sponsored healthcare benefits, items or services; and
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Violation of the laws described above or any other governmental laws and regulations may result in penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of operations, the exclusion from participation in federal and state healthcare programs, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, and imprisonment. Furthermore, efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we may obtain regulatory approval. In the United States, sales of any product candidates for which regulatory approval for commercial sale is obtained will depend in part on the availability of coverage and adequate reimbursement from third-party payors. Third-party payors include government authorities and health programs in the United States such as Medicare and Medicaid, managed care providers, private health insurers and other organizations. These third-party payors are increasingly reducing reimbursements for medical products and services. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all FDA-approved drugs for a particular indication. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. EU member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, 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 competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations may not allow favorable reimbursement and pricing arrangements.

Health Reform

The United States and some foreign jurisdictions are considering or have enacted a number of reform proposals to change the healthcare system. There is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, for example, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected and continues to face major uncertainty due to the status of major legislative initiatives surrounding healthcare reform. On August 16, 2022, the Inflation Reduction Act of 2022 (“IRA”) was signed into law. The IRA includes several provisions to lower prescription drug costs for people with Medicare and reduce drug spending by the federal government, including allowing Medicare to negotiate prices for certain prescription drugs, requiring drug manufacturers to pay a rebate to the federal government if prices for single-source drugs and biologicals covered under Medicare Part B and nearly all covered drugs under Part D increase faster than the rate of inflation (CPI-U), and limiting out of pocket spending for Medicare Part D enrollees. Additionally, On October 14, 2022, President Biden signed Executive Order 14087 on “Lowering Prescription Drug Costs for Americans.” The Executive Order specifically requests that the Center for Medicare and Medicaid Innovation consider “models that may lead to lower cost sharing for commonly used drugs and support value-based payment that supports high-quality care.”

Additional Regulation

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

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act ("FCPA") prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business abroad or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

Human Capital

As of February 20, 2023, we had 210 full-time employees, primarily engaged in research and development, manufacturing, administrative activities, and activities in preparation of commercialization of B-VEC. None of our employees are represented by a labor union and we consider our employee relations to be good.

We believe our employees are among the most important assets to our company and are key to achieving our goals and expectations. Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, and incentivizing our existing and new employees. We offer robust compensation packages, including competitive base pay, incentive compensation and stock compensation programs, and provide a broad range of benefits. The principal purpose of our stock compensation program is to attract, retain and reward personnel through the granting of stock-based awards, in order to increase stockholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives. In addition, we are committed to the professional advancement of our employees and offer various training programs and career development opportunities.

Corporate Information

We commenced operations in April 2016. In March 2017, we converted from a California limited liability company to a Delaware C-corporation, and changed our name from Krystal Biotech, LLC to Krystal Biotech, Inc. Our principal offices are located at 2100 Wharton Street, Suite 701, Pittsburgh, PA 15203, and our telephone number is 412-586-5830. In June 2018, the Company incorporated an Australian subsidiary, for the purpose of undertaking preclinical and clinical studies in Australia. In April 2019, the Company incorporated Jeune Aesthetics, Inc. in Delaware, a wholly-owned subsidiary, for the purpose of undertaking preclinical studies for aesthetic skin conditions. In January 2022, August 2022 and December 2022, we incorporated subsidiaries in Switzerland, Netherlands, and France, respectively, for the purpose of establishing initial operations in Europe for the development and commercialization of Krystal's pipeline. Our website address is www.krystalbio.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this Annual Report on Form 10-K. You should not rely on any such information in making your decision whether to purchase our common stock. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge on the investor relations section of our website as soon as reasonably practicable after we electronically file such material with, or furnish it to the Securities and Exchange Commission, or the SEC. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding the Company that we file electronically with the SEC. The address of the website is http://www.sec.gov.

Item 1A. Risk Factors.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred net losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred recurring losses and negative cash flows from operations and, at December 31, 2022, we had an accumulated deficit of $280.8 million. Our ability to achieve profitability depends on our ability to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize our product candidates. We have devoted substantially all our efforts to date to research and development of our gene therapy product candidates as well as to building out our infrastructure. We expect to continue to incur significant expenses and operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if, and as, we:

- continue our research and the clinical development of our product candidates, including our current clinical trials and planned future trials;
- initiate clinical trials for certain of our product candidates and preclinical studies for any additional product candidates that we may pursue in the future;
- prepare for regulatory approvals for our product candidates in the United States, EU and in other key geographies;
- continue to operate our in-house commercial-scale CGMP manufacturing facility, ANCORIS, and complete build out and startup of operations at our second CGMP manufacturing facility, ASTRA;
- manufacture material for clinical trials or potential commercial sales;
- further develop our gene therapy product candidate portfolio;
- further establish a sales, marketing and distribution infrastructure to commercialize any product candidate for which we may obtain marketing approval;
- develop, maintain, expand and protect our intellectual property portfolio; and
- acquire or in-license other product candidates and technologies,

To become and remain profitable, we must develop and eventually commercialize one or more product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing the clinical trials for our product candidates, developing and validating commercial scale manufacturing processes, obtaining marketing approval, manufacturing, marketing and selling any product candidates for which we may obtain marketing approval and satisfying any post-marketing requirements. If we were required to discontinue development of any of our product candidates, if any of our product candidates do not receive regulatory approval, if we do not obtain our targeted indications for our product candidates or if any of our product candidates fails to achieve sufficient market acceptance for any indication, we could be delayed by many years in our ability to achieve profitability, if ever, and would materially adversely affect our business prospects and financial condition. Moreover, if we decide to leverage any success with any of our current product candidates to develop other product opportunities, we may not be successful in such efforts. In any such event, our business will be materially adversely affected.

We currently have several product candidates in the clinical trials stages, but we may never develop, acquire or in-license additional product candidates. We may never succeed in any or all these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease 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.

Because of the numerous risks and uncertainties associated with pharmaceutical product and biological development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA, the EMA, or other regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of our product candidates, our expenses could increase and revenue from product candidates in development and profitability from commercially available products could be further delayed.

We may need to raise additional funding in order to receive approval for our product candidates. Such funding may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development efforts or other operations.

To complete the process of obtaining regulatory approval for our product candidates and to continue building the sales, marketing and distribution infrastructure that we believe will be necessary to commercialize our product candidates, if approved, we may require substantial additional funding. In addition, if we obtain marketing approval for our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. We anticipate that we may need additional funding to complete the development of our product candidates and to commercialize any such approved products.

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

- the length of our open label study for B-VEC;
- the progress, timing results and costs of our Phase 1/2 clinical trials for KB105;
- the progress, timing, results and costs of our Phase 2 clinical trials for KB301;
- the progress, timing, results and costs of our Phase 1 clinical trials for KB407;
- the continued development and the filing of IND applications for KB104 and other product candidates;
- the initiation, scope, progress, timing, costs and results of drug discovery, laboratory testing, manufacturing, preclinical studies and clinical trials for any other product candidates that we may pursue in the future, if any;
- the costs of building and maintaining our own commercial-scale CGMP manufacturing facilities;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs associated with the manufacturing process development and evaluation of third-party manufacturers, if necessary;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing and distribution, in the event we receive marketing approval for any of our current and future product candidates;
- the extent to which the costs of our product candidates, if approved, will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors;
- subject to receipt of marketing approval, if any, revenue received from commercial sale of our current and future product candidates;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish;
- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, maintenance, defense and enforcement of any patents or other intellectual property rights, including milestone and royalty payments and patent prosecution fees that we are obligated to pay pursuant to our license agreements, if any;
- our current license agreements, if any, remaining in effect and our achievement of milestones under those agreements;
- our ability to establish and maintain collaborations and licenses on favorable terms, if at all; and
- the extent to which we acquire or in-license other product candidates and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales for our product candidates in development. Furthermore, even if we obtain approval for a product candidate, we may not be able to successfully generate significant revenue from the sale of such product candidate. Accordingly, we may need to continue to rely on additional financing to achieve our business objectives. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all our stockholders. Existing stockholders may not agree with our financing plans or the terms of such financings. Adequate additional financing may not be available to us on acceptable terms, or at all. The terms of additional

financing may be impacted by, among other things, general market conditions, the market's perception of our product candidates and growth potential and the market price per share of our common stock. See "Raising additional capital could cause the price of our common stock to decline and cause dilution to our stockholders, restrict our operations or require us to relinquish rights."

Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

We have U.S. federal and state net operating loss carryforwards, which are available to reduce future taxable income. Federal net operating loss carryforwards generated 2018 through 2021 will be limited to offset 80% of taxable income for an indefinite period of time, until fully utilized. These federal and state net operating loss carryforwards expire beginning in 2037. We also have federal and state research and development tax credits which may be used to offset future tax liabilities and expire beginning in 2039 and 2032, respectively. We also have federal orphan drug tax credits which may be used to offset future tax liabilities which expire beginning in 2038.

Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, changes in our ownership may limit the amount of our net operating loss carryforwards and tax credit carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation may significantly reduce our ability to utilize our net operating loss carryforwards and tax credit carryforwards before they expire. Private placements and other transactions that have occurred since our inception, as well as our initial public offering, may trigger such an ownership change pursuant to Sections 382 and 383. Any such limitation, whether as the result of the initial public offering, prior private placements, sales of our common stock by our existing stockholders or additional sales of our common stock by us, could have a material adverse effect on our results of operations in future years. Generally, under current law, federal net operating losses generated after December 31, 2017 are not subject to expiration and may not be carried back to prior taxable years. However, the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, suspended the 80% taxable income limitation for net operating losses generated in 2018, 2019, and 2020 to the extent these losses are exhausted during the special five-year carryback period or during the 2018, 2019 or 2020 tax years. Additionally, as noted above, for taxable years beginning after December 31, 2020, the CARES Act provisions no longer apply and the deductibility of such federal net operating losses is limited to 80% of our taxable income in any future taxable year.

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

We commenced operations in 2016. Our efforts to date, with respect to the development of our product candidates have been limited to organizing and staffing our company, business planning, raising capital, developing our vector platform and related technologies, identifying potential gene therapy product candidates, and undertaking preclinical studies and clinical trials. We have not yet demonstrated an ability to obtain marketing approvals for any of our products, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success, performance or viability may not be as accurate as they could be if we had more experience developing gene therapy products.

We expect our financial condition and operating results to continue to fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. We will need to transition from a company with a research and development focus to a company capable of undertaking commercial activities. We may encounter unforeseen expenses, difficulties, complications and delays and may not be successful in such a transition. Accordingly, you should not rely upon the results of any particular quarterly or annual period as indications of future operating performance.

Risks Related to Our Business

We are substantially dependent on the commercial success of B-VEC

To date, we have invested substantial efforts and financial resources in the research and development of our product candidates. Our near-term prospects, including our ability to develop our product candidates and generate revenue, and our future growth is substantially dependent on the commercial success of B-VEC. We initiated Phase 3 testing of B-VEC in July of 2020 and announced positive topline results in November 2021. We submitted the BLA for B-VEC in June 2022, which was accepted by the FDA in August 2022 and granted priority review. The PDUFA target date is May 19, 2023, but we cannot be certain of how long it will take to successfully complete the regulatory approval process.

Any delay in obtaining FDA approval of the BLA for B-VEC would further delay commercialization and would adversely impact our ability to generate revenue and further develop our other product candidates. If the BLA for B-VEC is not approved on a timely basis or at all, our business, financial condition, results of operations and prospects would be adversely impacted. The successful development, regulatory approval and commercialization of B-VEC will depend on a number of

factors, including the risks identified in these "Risk Factors." One or more of these factors, many of which are beyond our control, could cause significant delays or an inability to successfully commercialize B-VEC. Accordingly, we cannot assure you that we will be able to generate revenue through the sale of B-VEC.

The effect of the COVID-19 pandemic or similar public health crises on our operations and the operations of our third-party partners could cause a disruption of the development efforts for our product candidates and adversely impact our business.

The COVID-19 pandemic has previously adversely affected our international business and could have a material adverse effect on our financial condition and results of operations. Authorities have previously imposed, and businesses and individuals have implemented, numerous measures to try to contain the virus or treat its impact, such as travel bans and restrictions, quarantines, shelter-in-place/stay-at-home and social distancing orders, shutdowns, and vaccine requirements. These measures have impacted and may further impact our workforce and operations, the operations of our customers, and those of our third-party partners.

The extent to which COVID-19 or similar public health crises impacts our operations or those of our third-party partners will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration of the pandemic, additional or modified government actions, new information that will emerge concerning the severity and impact of COVID-19, including new strains, and the actions to contain COVID-19 or address its impact in the short and long term, among others.

Timely initiation and completion of planned clinical trials is dependent upon the availability of, for example, clinical trial sites, researchers and investigators, regulatory agency personnel, and materials, which may be adversely affected by global health matters, such as pandemics.

In the event that governmental authorities were to further modify or implement new restrictions, our employees conducting research and development or manufacturing activities may not be able to access our laboratory or manufacturing spaces, and our core activities may be significantly limited or curtailed, possibly for an extended period of time.

If we are unable to advance our product candidates through clinical trials, obtain regulatory approval and ultimately commercialize our product candidates, or if we experience significant delays in doing so, our business will be materially harmed.

The development and commercialization of our product candidates are subject to many uncertainties, including the following:

- successful enrollment and completion of clinical trials;
- positive results from our current and planned future clinical trials;
- receipt of regulatory approvals from applicable regulatory authorities;
- successful development of our internal manufacturing processes on an ongoing basis and maintenance of our existing arrangements with third-party manufacturers for clinical supply;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of our product candidates, if and when approved, by patients, the medical community and third-party payors;

If we fail in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. If we do not receive regulatory approvals for our product candidates, our business, financial condition, results of operations and prospects could be materially and adversely affected.

Our lead candidate, B-VEC, has not received regulatory approval, and if we obtain regulatory approval to commercialize B-VEC the approval may be for a narrower indication than we seek.

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. In June 2022, we filed a BLA with the FDA seeking approval of B-VEC for the treatment of patients with DEB with a request for six-month priority review. In August 2022, the FDA accepted the BLA and granted priority review with a PDUFA target date of February 17, 2023. In January 2023, the FDA notified us that based on manufacturing information submitted to the agency on December 20, 2022, in response to an information request, the PDUFA date had been revised to May 19, 2023. Even though B-VEC met its safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval.

Additionally, we submitted a request for MAA with the EMA in November 2022 for B-VEC for the treatment of DEB in patients 6 months and older. The Company was informed by the EMA in January 2023 to modify the PIP waiver request to include patients between birth and 6 months. The Company is modifying the application so that the MAA procedure can officially start in the second half of 2023 with an approval expected in early 2024.

Regulatory authorities also may approve a product candidate for more limited indications than requested or they may impose significant limitations in the form of narrow indications, warnings or a post-approval safety monitoring program. These regulatory authorities may require precautions or contra-indications with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of B-VEC. Any of the foregoing scenarios could materially harm the commercial prospects for B-VEC and materially and adversely affect our business, financial condition, results of operations and prospects.

B-VEC is based on a novel technology, which makes it difficult to predict the time and cost of obtaining regulatory approval.

The clinical trial requirements of the FDA, EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or how long it will take to commercialize our product candidates. Approvals by the European Commission may not be indicative of what FDA may require for approval and approval by the FDA may not be indicative of what the European Commission would require for approval.

Regulatory requirements and policy governing gene and cell therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Tissues and Advanced Therapies within its CBER to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. If we were to engage a National Institutes of Health funded institution to conduct a clinical trial, that institution's IBC as well as its IRB, would need to review the proposed clinical trial to assess the safety of the trial. Similarly, the EMA may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of B-VEC or future product candidates or lead to significant post-approval limitations or restrictions. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

Our products may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

There have been several significant adverse side effects in gene therapy trials using other vectors in the past. Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

In addition to side effects caused by the product candidate, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur, our clinical trials could be suspended or terminated. If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, the FDA, the European Commission, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our products for any or all targeted indications. Even if we can demonstrate that any serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of our products, the commercial prospects of such product candidate may be harmed and our ability to generate product revenues from the product candidate may be delayed or eliminated. Any of these occurrences may harm our ability to develop product candidates, and may harm our business, financial condition and prospects significantly.

Additionally, if one of our product candidates receives marketing approval, the FDA could require us to adopt a post-approval safety monitoring program to ensure that the benefits outweigh its risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients and a communication plan to health care practitioners. Furthermore, if we or others later identify undesirable side effects caused by our product candidates, several potentially significant negative consequences could result, including:

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

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, financial condition, results of operations and prospects.

We may encounter substantial delays in our clinical trials, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidate for its intended indications. Clinical trials are expensive, time consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory authorities on trial design;
- delays in opening sites and recruiting a sufficient number and diversity of suitable patients to participate in our clinical trials;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or concerns with a class of product candidates, or after an inspection of our clinical trial operations or trial sites;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

In addition, if we make manufacturing or formulation changes to our products, we may need to conduct additional studies to bridge our modified product candidate to earlier versions. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our products or allow our competitors to bring products to market before we do, which could limit our potential revenue or impair our ability to successfully commercialize our products and may harm our business, financial condition, results of operations and prospects. Any delays, setbacks or failures in our clinical trials could materially and adversely affect our business, financial condition, results of operations and prospects.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval, if at all, or be required to conduct additional confirmatory safety and/or efficacy studies;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements;
- be required to perform additional clinical trials to support approval;
- have regulatory authorities withdraw, or suspend, their approval of the product or impose restrictions on its distribution;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or

- experience damage to our reputation.

Our product development costs will also increase if we experience delays in testing or obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, need to be restructured or be completed on schedule, if at all.

Further, we, the FDA or an IRB, may suspend our clinical trials at any time if it appears that we or our collaborators are failing to conduct a trial in accordance with regulatory requirements, including the FDA's current GCP regulations, that we are exposing participants to unacceptable health risks, or if the FDA finds deficiencies in our IND applications or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be negatively impacted, and our ability to generate revenues from our product candidates may be delayed.

Even if we obtain regulatory approval for a product candidate, our product candidates will remain subject to regulatory oversight. We will continue to incur costs related to regulatory compliance and are subject to risks related to non-compliance with or changes to applicable law and regulations, which would cause our product candidates to lose approval.

Even if we obtain any regulatory approval for B-VEC, our lead product candidate, or other future product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates may also be subject to a post-approval safety monitoring program, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with CGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, 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 or a regulatory authority disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements, a regulatory authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners, if any;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of product candidates; or
- refuse to allow us to enter into supply contracts, including government contracts.

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

The FDA's policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in

the United States or abroad. 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 and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

While we have obtained orphan drug designation for B-VEC, KB105, and KB407, it may not effectively protect us from competition, and we may be unable to obtain orphan drug designation for our future product candidates. If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates before us, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

On November 2, 2017, the FDA granted orphan drug designation to our lead product candidate, B-VEC, for the treatment of DEB. On April 16, 2018, the European Commission granted the Orphan Medicinal Product Designation ("OMPD"), for B-VEC. On August 7, 2018, the FDA granted orphan drug designation to our product candidate, KB105, currently in clinical development for treatment of patients with TGM1-ARCI, and on October 10, 2019, the European Commission granted the OMPD for KB105. On August 17, 2020, the FDA granted orphan drug designation to our product candidate, KB407, currently in clinical development, for the treatment of cystic fibrosis, and on January 13, 2023, the European Commission granted the OMPD for KB407. Regulatory authorities in some jurisdictions, including the United States and the EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the European Commission, upon a recommendation from the EMA's Committee for Orphan Medicinal Products, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug or biologic product.

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

Even though we have obtained orphan drug exclusivity for B-VEC, KB105 and KB407, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the EU, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although like the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply enough quantities of orphan medicinal product.

Breakthrough therapy designation, Regenerative Medicine Advanced Therapy designation, Fast Track designation or Rare Pediatric Disease designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development, regulatory review or approval process, and it does not increase the likelihood that any of our product candidates will receive marketing approval in the United States.

The FDA granted Fast Track designation in the United States for B-VEC and for KB105. In addition, B-VEC was granted RMAT by the FDA and PRIME by the EMA. The receipt of any of these designations for a product candidate may not result in a faster development process, review or approval compared to products considered for approval under conventional FDA and EMA procedures and does not assure ultimate approval by either the FDA or EMA.

A RMAT/PRIME therapy product candidate is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease. Drugs designated as RMAT therapies by the FDA are eligible for accelerated approval and increased interaction and communication with the FDA designed to expedite the development and review process. If a drug, or biologic in our case, is intended for the treatment of a serious or life-threatening condition and the biologic demonstrates the potential to address unmet medical needs for this condition, the biologic sponsor may apply for FDA Fast Track designation. Even after having received Fast Track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. 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. Many biologics that have received Fast Track designation have failed to obtain approval. A sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. We received the designation of "rare pediatric disease" for B-VEC, KB105, KB104, and for KB407, which could qualify us to receive a Rare Pediatric Priority Review Voucher.

There is no assurance we will receive RMAT, PRIME or breakthrough therapy or Fast Track designations for any of our other product candidates and the receipt of any of these designations for a product candidate may not result in a faster development process, review or approval and does not assure ultimate approval by the FDA. Further, even though we have received rare pediatric disease designation for B-VEC, KB105, KB104, and KB407, we may not experience a faster review or approval for a subsequent marketing application.

We may expend our limited resources to pursue a product candidate or indication to the exclusion of other product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

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

If we are not successful in discovering, developing and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

Although a substantial amount of our efforts focuses on the potential approval of B-VEC, KB105, KB301, KB104 and KB407, a key component our strategy is to discover, develop and potentially commercialize a portfolio of product candidates to treat orphan diseases and ultimately, non-orphan diseases. Identifying new product candidates requires substantial technical, financial and human resources, whether any product candidates are ultimately identified. Even if we identify product candidates that initially show promise, we may fail to successfully develop and commercialize such product candidates for many reasons, including the following:

- 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 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; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors.

If we are unsuccessful in identifying and developing additional product candidates, our potential for growth may be impaired.

We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize and market our product candidates.

We are aware of several companies and institutions that are currently developing alternative autologous or palliative gene therapy approaches for DEB and cystic fibrosis. Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunities could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidate that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render B-VEC or any future product candidate uneconomical or obsolete, and we may not be successful in marketing B-VEC or any future product candidate against competitors.

In the future, even if we commercialize a product candidate faster than our competitors, we could also face competition from lower cost biosimilars in the United States or in Europe.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any product candidate that we may develop and commercialize.

If any product liability lawsuits are successfully brought against us, we may incur substantial liabilities and may be required to limit commercialization of our products or product candidates.

We face an inherent risk of product liability lawsuits related to the sale of our products to, use of our products by, and testing of our product candidates. Product liability claims may be brought against us by participants enrolled in our clinical trials, patients, health care providers or others using, or administering any of our approved products. If we cannot successfully defend ourselves against any such claims, we may incur substantial liabilities. Regardless of their merit or eventual outcome, liability claims may result in:

- decreased demand for our approved products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- increased regulatory scrutiny;
- significant litigation costs;
- substantial monetary awards to or costly settlement with patients or other claimants;
- product recalls for approved products or a change in the indications for which they may be used;
- loss of revenue;
- diversion of management and scientific resources from our business operations; and
- the inability to commercialize our product candidates.

With respect to any of our product candidates that are approved for commercial sale, we are, and will be, highly dependent upon physician and patient perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity. We could also be adversely affected if any of our products or any similar products distributed by other companies prove to be, or are asserted to be, harmful to patients. Because of our dependence upon consumer perceptions, any adverse publicity could have a material adverse impact on our financial condition or results of operations.

Our product liability insurance coverage may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage when we begin the commercialization of our product candidates. Insurance coverage is becoming increasingly expensive. As a result, we may be unable to maintain or obtain sufficient insurance at a reasonable cost to protect us against losses that could have a material adverse effect on our business. A successful product liability claim or

series of claims brought against us, particularly if judgments exceed any insurance coverage we may have, could decrease our cash resources and adversely affect our business, financial condition and results of operations.

Risks Related to Manufacturing

Delays in obtaining regulatory approvals of the process and facilities needed to manufacture our product candidates or disruptions in our manufacturing process may delay or disrupt our product development and commercialization efforts.

Before we can begin to commercially manufacture our product candidates, we must pass a pre-approval inspection of our manufacturing facilities by the FDA. A manufacturing authorization must also be obtained from the appropriate EU regulatory authorities. The timeframe required for us to obtain such approvals is uncertain. To obtain approval, we will need to ensure that all our processes, methods and equipment are compliant with CGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with CGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The CGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with CGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any product candidate that we may develop.

In addition, the manufacturing process used to produce our product candidates is complex, novel and has not been validated for commercial use. In order to produce enough quantities of our product candidates for future clinical trials and initial U.S. commercial demand, we will need to increase the scale of our manufacturing process. The production of our product candidates requires processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we employ multiple steps to control our manufacturing process to assure that the process works and that our product candidates are made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

Although we have established our own manufacturing facilities for our product candidates, we may also utilize third parties to conduct our product manufacturing. Therefore, we are subject to the risk that these third parties may not perform satisfactorily.

Even if we obtain the validation from the FDA of our CGMP manufacturing facilities, we may maintain third-party manufacturing capabilities in order to provide multiple sources of supply. We utilize a third-party for manufacturing of the sterile gel that is mixed with our in-house produced vector. In the event that these third-party manufacturers do not successfully carry out their contractual duties, meet expected deadlines or manufacture in accordance with regulatory requirements or if there are disagreements between us and these third-party manufacturers, we may not be able to manufacture our products for commercial or regulatory purposes. In such instances, we may need to locate an appropriate replacement third-party relationship, which may not be readily available or on acceptable terms, which would cause additional delay or increased expense and would thereby have a material adverse effect on our business, financial condition, results of operations and prospects.

If we or a third-party manufacturer fails to comply with applicable CGMP regulations, the FDA and foreign regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be materially harmed.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our ability to produce our product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or

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

Risks Related to Commercialization of Our Product Candidates

If we are unable to expand our market development capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any product revenue.

To successfully commercialize B-VEC, and any other approved product candidates, we have expanded our capabilities to promote market access and build awareness. To successfully commercialize any products that may result from our development programs, we will need to further expand our market development organization, either on our own or with a third-party. The development of our own market development team is expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may enter into collaboration agreements regarding any of our product candidates with third parties to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. Without an internal team or the support of a third-party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our products. If any of our product candidates is approved but fails to achieve market acceptance among physicians, patients or third-party payors, we will not be able to generate significant revenues from such product, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

We have mainly focused our research and product development efforts to date on B-VEC for DEB. Our understanding of both the number of people who have this disease, as well as the subset of people with this disease who have the potential to benefit from treatment with B-VEC, are based on estimates in published literature. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of this disease. The number of patients in the United States, the EU and elsewhere may turn out to be lower than expected or these patients may not be otherwise amenable to treatment with B-VEC or may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive B-VEC less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment

will likely diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell damage. Lastly, certain patients' immune systems might prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

The commercial success of our product candidates will depend upon their degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even with the requisite approvals from the FDA in the United States, the EMA in the EU and other regulatory authorities internationally, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidates, in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of gene therapy products and our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy and safety of our product candidates as demonstrated in clinical trials;
- the efficacy, potential and perceived advantages of our product candidates over alternative treatments, if available;
- the cost of our product candidates relative to alternative treatments, if any are available;
- the clinical indications for which our product candidates are approved by the FDA or the EMA;
- the willingness of physicians to prescribe new therapies;
- the willingness of the target patient population to try new therapies;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA, the EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of products and their ability to meet market demand;
- publicity concerning our product candidates or competing products and treatments;
- any restrictions on the use of our products together with other medications; and
- favorable third-party payor coverage and adequate reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched.

Government price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates, if approved, which would adversely affect our revenue and results of operations.

We expect that coverage and reimbursement of pharmaceuticals may be increasingly restricted both in the U.S. and internationally. The escalating cost of health care has led to increased pressure on the health care industry to reduce costs. Drug pricing by pharmaceutical companies recently has come under increased scrutiny and continues to be subject to intense political and public debate in the U.S. and abroad. Government and private third-party payors have proposed health care reforms and cost reductions. A number of federal and state proposals to control the cost of health care, including the cost of drug treatments, have been made in the U.S. Specifically, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. In some international markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding health care may affect coverage and reimbursement for medical treatment by third-party payors, which may render our product candidates, if approved, not commercially viable or may adversely affect our anticipated future revenues and gross margins.

We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, future price controls or other changes in pricing regulation or negative publicity related to

the pricing of pharmaceutical drugs generally could restrict the amount that we are able to charge for our future products, which would adversely affect our anticipated revenue and results of operations.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our products, if approved, could limit our ability to market those products and decrease our ability to generate product revenue.

We expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford our products. Accordingly, sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several 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.

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment.

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products. In the United States, third-party payors, including government payors such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payors and government payors develop their coverage and reimbursement policies. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these types of products. Moreover, reimbursement agencies in the European Union may be more conservative than CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European Union Member States. It is difficult to predict what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Outside the United States, international operations generally are subject to extensive government price controls and other market regulations and increasing emphasis on cost-containment initiatives in the EU, Canada and other countries may put pricing pressure on us. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. It also can take a significant amount of time after approval of a product to secure pricing and reimbursement for such product in many counties outside the United States. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues.

Moreover, increasing efforts by government and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. Payors increasingly are considering new metrics as the basis for reimbursement rates, such as Average Sales Price, Average Manufacturer Price, and Actual Acquisition Cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. Therefore, it may be difficult to project the impact of these evolving reimbursement metrics on the willingness of payors to cover candidate products that we are able to commercialize. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional potential legislative and administrative changes. The downward

pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours.

Ethical, legal and social issues related to genetic testing may reduce demand for our product candidates, if approved.

We anticipate that prior to receiving certain gene therapies, patients may be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been expressed that insurance carriers and employers may use these tests to discriminate based on genetic information, resulting in barriers to the acceptance of genetic tests by consumers. Concerns have also been raised about the accuracy of genetic testing. This could lead to governmental authorities restricting genetic testing or calling for additional regulation of genetic testing, particularly for diseases for which there is no known cure. Any of these scenarios could decrease demand for our product candidates, if approved.

Even if we obtain and maintain approval for our product candidates from the FDA, we may never obtain approval for them outside of the United States, which would limit our market opportunities and adversely affect our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of B-VEC or other future product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our product candidates, if approved, is also subject to approval. Obtaining a Marketing Authorization Application from the European Commission following the opinion of the EMA is a lengthy and expensive process. We submitted a request for MAA with the EMA in November 2022 for B-VEC for the treatment of DEB in patients 6 months and older. The Company was informed by the EMA in January 2023 to modify the PIP waiver request to include patients between birth and 6 months. The Company is modifying the application so that the MAA procedure can officially start in the second half of 2023 with an approval expected in early 2024. Even if a product candidate is approved, the FDA or the European Commission, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the EU also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. 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 product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be adversely affected.

Increasing demand for compassionate use or expanded access of our unapproved therapies could negatively affect our reputation and harm our business.

We are developing our product candidates for illnesses for which there are currently limited to no available therapeutic options. At least one other company has been the target of disruptive social media campaigns related to a request for access to unapproved drugs for patients with significant unmet medical need. If we experience a similar social media campaign regarding our decision to provide or not provide our product candidates under an expanded access corporate policy, our reputation may be negatively affected and our business may be harmed. Recent media attention to individual patients' expanded access requests has resulted in the introduction of legislation at the local and national level referred to as "Right to Try" laws, such as the Right to Try Act, which are intended to give patients access to unapproved therapies. New and emerging legislation regarding expanded access to unapproved drugs for life-threatening illnesses could negatively impact our business in the future.

A possible consequence of both activism and legislation in this area is the need for us to initiate an unanticipated expanded access program or to make our product candidates more widely available sooner than anticipated. We are a small company with limited resources and unanticipated trials or access programs could result in diversion of resources from our primary goals.

In addition, some patients who receive access to unapproved drugs through compassionate use or expanded access programs have life-threatening illnesses and have exhausted all other available therapies. The risk for serious adverse events in this patient population is high which could have a negative impact on the safety profile of our product candidates if we were to provide them to these patients in accordance with our expanded access corporate policy, which could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business. If we were to provide patients with our product candidates under our expanded access corporate policy, we may in the future need to restructure or pause ongoing compassionate use and/or expanded access programs in order to perform the controlled clinical trials required for regulatory approval and successful commercialization of our product candidates, which could prompt adverse publicity or other disruptions related to current or potential participants in such programs.

Risks Related to Our Business Operations

We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.

The success of our business depends upon our ability to identify, develop and commercialize product candidates based on our gene therapy platform. Research programs to identify new product candidates require substantial technical, financial and human resources. Although certain of our product candidates are currently in clinical or preclinical development, we may fail to identify other potential product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have commercial potential. Our spending on current and future research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We have experienced significant growth in the number of employees and infrastructure and may experience difficulties in managing this growth. If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

We have experienced a period of significant expansion in personnel and of our facilities, infrastructure and overhead as we develop our own manufacturing facilities, build our sales, marketing and distribution infrastructure that we believe will be necessary to commercialize B-VEC, and increase our research and development efforts. The anticipated commercialization of B-VEC and our ongoing development of other product candidates, will continue to impose significant added capital requirements, as well as added responsibilities on members of management, including the need to identify, recruit, maintain and integrate new personnel. Our future financial performance and our ability to compete effectively will depend, in part, on our ability to manage our growth effectively. If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain enough numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

Our future success depends on our ability to retain key employees and scientific advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on members of our management team, the loss of whose services may adversely impact the achievement of our objectives. Our employees and scientific advisors are at-will employees and consultants, and the loss of one or more of them might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining other qualified employees and scientific advisors for our business, including scientific and technical personnel, also will be critical to our success. There currently is a shortage of skilled individuals with substantial gene therapy experience, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of certain executives, key employees or advisors, may impede the progress of our research, development and commercialization objectives and have a material adverse effect on our business, financial condition, results of operations and prospects.

Our employees, principal investigators and advisors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators and advisors. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions, provide accurate information to the FDA, the EMA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. Sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in criminal and civil penalties or sanctions and cause serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant fines, criminal penalties, or other sanctions.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of our current and future drug candidates.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

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 our product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the U.S., there have been and continue to be a number of legislative efforts to contain healthcare costs. For example, in March 2010, PPACA, as amended by the Health Care and Education Reconciliation Act, was passed, which substantially changed the way healthcare is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The PPACA, among other things: (i) addresses 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; (ii) increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations; (iii) establishes annual fees and taxes on manufacturers of certain branded prescription drugs; (iv) expands the availability of lower pricing under the 340B drug pricing program by adding new entities to the program; and (v) establishes a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand

drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the PPACA, and we expect there will be additional challenges in the future. As a result, there have been delays in the implementation of, and action taken to repeal or replace, certain aspects of the PPACA. Most recently, under President Biden, the Department of Justice dropped support of two Supreme Court cases challenging the PPACA in addition to a case before the U.S. Court of Appeals for the Fifth Circuit, and in June 2021, the Supreme Court upheld the PPACA in a 7-2 opinion that the states and individuals that challenged the individual mandate did not have standing to challenge the law. Further, on January 28, 2021, President Biden signed an executive order to expand access to PPACA coverage, stating that it is the "policy" of the Biden administration to protect and strengthen the PPACA and directing agencies to consider suspending, revising, or rescinding actions related to President Trump's executive orders that are inconsistent with this policy position. However, other legislators continue efforts to repeal and replace other elements of the PPACA. While the ultimate outcome of PPACA result of these efforts is not yet known, any changes that result in price controls reduce access to and reimbursement for care or add additional regulations may have an adverse effect on our financial condition and results of operations.

We cannot predict the impact that such actions against the PPACA or other health care reform under the Biden administration will have on our business, and there is uncertainty as to what healthcare programs and regulations may be implemented or changed at the federal and/or state level in the United States, or the effect of any future legislation or regulation. However, it is possible that such initiatives could have an adverse effect on our ability to obtain approval and/or successfully commercialize products in the United States in the future. For example, any changes that reduce, or impede the ability to obtain, reimbursement for the type of products we intend to commercialize in the United States (or our products more specifically, if approved) could adversely affect our business plan to introduce our products in the United States.

While Congress has not passed repeal legislation, the Tax Reform Act includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Further, the Bipartisan Budget Act of 2018, among other things, amended the PPACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress may consider other legislation to repeal and replace elements of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

Other legislative changes have been proposed and adopted in the United States since the PPACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to certain providers, and increased the time for Medicare contractors to recoup Medicare overpayments to providers from three to five years. On August 16, 2022, the Inflation Reduction Act of 2022 ("IRA") was signed into law. The IRA includes several provisions to lower prescription drug costs for people with Medicare and reduce drug spending by the federal government. In relevant part, the IRA allows Medicare to negotiate prices for certain prescription drugs, requires drug manufacturers to pay a rebate to the federal government if prices for single-source drugs and biologicals covered under Medicare Part B and nearly all covered drugs under Part D increase faster than the rate of inflation ("CPI-U") and caps out of pocket spending for Medicare Part D enrollees and makes other benefit design changes to Medicare Part D intended to lower drug costs for enrollees and Medicare. These requirements, which begin to go into effect in 2023, will affect the amounts available through reimbursement for Medicare programs. These significant changes made under the IRA, which will affect pricing for both brand and generic drugs, may affect reimbursement for our products.

Further, there has been heightened governmental scrutiny in recent years over the manner in which manufacturers set prices for their marketed products and the cost of prescription drugs to consumers and government healthcare programs, which have resulted in several recent Congressional inquiries and proposed and enacted bills designed to, among other things, reduce the cost of prescription drugs, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. In addition, the United States government, state legislatures, and foreign governments have shown significant interest in implementing cost containment programs, including price-controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs to limit the growth of government paid health care costs. For example, the United States government has passed legislation requiring pharmaceutical manufacturers to provide rebates and discounts to certain entities and governmental payors to participate in federal healthcare programs. Individual states in the United States have also

been increasingly passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Additional changes may affect our business, including those governing enrollment in federal healthcare programs, reimbursement changes, fraud and abuse enforcement, and expansion of new programs, such as Medicare payment for performance initiatives. On October 14, 2022, President Biden signed Executive Order 14087 on "Lowering Prescription Drug Costs for Americans." The Executive Order specifically requests that the Center for Medicare and Medicaid Innovation consider "models that may lead to lower cost sharing for commonly used drugs and support value-based payment that supports high-quality care." The outcomes of the findings made under the Executive Order could lead to further drug pricing initiatives that could affect reimbursement for our products.

These initiatives, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms could result in reduced demand for our product candidates or additional pricing pressures and may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for our product candidates and begin commercializing them in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Anti-Kickback Statute, federal civil and criminal false claims laws and the Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business as well as other jurisdictions. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, in return for the purchase, recommendation, leasing or furnishing of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amended the intent requirement of the federal Anti-Kickback Statute to clarify that a person or entity does not have to have actual knowledge of this statute or specific intent to violate it;
- federal civil and criminal false claims laws and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent. The PPACA provides that a claim for items or services resulting from an Anti-Kickback Statute violation is a false claim under the federal FCA. Cases against pharmaceutical manufacturers support the view that certain marketing practices, including off-label promotion, may implicate the FCA;
- the federal Health Care Fraud statute imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("HITECH"), and its implementing regulations, and as amended again by the final HIPAA omnibus rule, Modifications to the HIPAA Privacy, Security, Enforcement, and Breach;
- Notification Rules under HITECH and the Genetic Information Nondiscrimination Act; Other modifications to HIPAA, published in January 2013, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses and health care providers;
- federal transparency laws, including the federal Physician Payment Sunshine Act, that require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the CMS

information related to: (i) payments or other "transfers of value" made to physicians and teaching hospitals and (ii) ownership and investment interests held by physicians and their immediate family members;

- state and foreign law equivalents of each of the above federal laws, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts in certain circumstances, such as specific disease states; and
- state and foreign laws that 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.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment 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.

Often, to avoid the threat of treble damages and penalties under the FCA, health care providers will resolve allegations in a settlement without admitting liability. Any such settlement could materially affect our business, financial operations, and reputation.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain a robust and expandable systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the possibility that a healthcare company may run afoul of one or more of the requirements.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biologic materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Moreover, certain environmental laws may impose liability without regard to fault or legality of the action at the time of its occurrence. We also could incur significant costs associated with civil or criminal fines and penalties. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

We also may incur substantial costs to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in

substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets, including conditions that are outside of our control. Inflation and rising interest rates have caused volatility in the capital and credit markets, and it is unclear how long such volatility will continue. A severe or prolonged economic downturn could result in a variety of risks to our business, including our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all the ways in which the current economic climate and financial market conditions could adversely impact our business.

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

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Cyber-security incidents, including data security breaches or computer viruses, could harm our business by disrupting our operations, damaging our reputation or exposing us to liability.

We receive, process, store, and transmit, often electronically, confidential data of others, including the participants in our clinical trials. Unauthorized access to our computer systems or stored data could result in the theft or improper disclosure of confidential information, the deletion or modification of records, or could cause interruptions in our operations. These cyber-security risks increase when we transmit information from one location to another, including transmissions over the Internet or other electronic networks. Despite implemented security measures, our facilities, systems, and procedures, and those of our third-party service providers, may be vulnerable to security breaches, acts of vandalism, software viruses, misplaced or lost data, programming and/or human errors, or other similar events which may disrupt our operations or expose confidential information of the patients who participate in our clinical trials. Any security breach involving the misappropriation, loss or other unauthorized disclosure or use of confidential information of others, whether by us or a third-party, could: (i) subject us to civil and criminal penalties; (ii) have a negative impact on our reputation; or (iii) expose us to liability to third parties or government authorities.

Our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Natural disasters could severely disrupt our operations or the operations of third-party suppliers or service providers and have a material adverse effect on our business, financial condition, results of operations and prospects. The severity and frequency of weather-related natural disasters have been amplified, and are expected to continue to be amplified by, global climate change. Such natural disasters may cause, damage to and/or disrupt our operations, which may result in a material adverse effect on our product sales, if approved, business and results of operations. Moreover, climate change may also result in various chronic physical changes, such as changes in temperature or precipitation patterns or sea-level rise, that may also have an adverse impact on our operations. Our suppliers, vendors and business partners also face similar risks, and any disruption to their operations could have an adverse effect on our supply and manufacturing chain. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our manufacturing facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans that we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Substantially all our current supply of our product candidates is located at our manufacturing facility in Pittsburgh, Pennsylvania. We are constructing an additional manufacturing facility for the commercial supply of our products. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Increased attention to, and evolving expectations for, environmental, social, and governance ("ESG") initiatives could increase our costs, harm our reputation, or otherwise adversely impact our business.

Companies across industries are facing increasing scrutiny from a variety of stakeholders related to their ESG and sustainability practices. Expectations regarding voluntary ESG initiatives and disclosures may result in increased costs (including but not limited to increased costs related to compliance, stakeholder engagement, contracting and insurance), enhanced compliance or disclosure obligations, or other adverse impacts to our business, financial condition, or results of operations.

While we may at times engage in voluntary initiatives (such as voluntary disclosures, certifications, or goals, among others) to improve the ESG profile of our company and/or products, such initiatives may be costly and may not have the desired effect. Moreover, we may not be able to successfully complete such initiatives due to factors that are within or outside of our control. Even if this is not the case, our actions may subsequently be determined to be insufficient by various stakeholders, and we may be subject to investor or regulator engagement on our ESG efforts, even if such initiatives are currently voluntary.

Certain market participants, including major institutional investors and capital providers, use third-party benchmarks and scores to assess companies' ESG profiles in making investment or voting decisions. Unfavorable ESG ratings could lead to increased negative investor sentiment towards us or our industry, which could negatively impact our share price as well as our access to and cost of capital. To the extent ESG matters negatively impact our reputation, it may also impede our ability to compete as effectively to attract and retain employees or customers, which may adversely impact our operations.

In addition, we expect there will likely be increasing levels of regulation, disclosure-related and otherwise, with respect to ESG matters. For example, the SEC has published proposed rules that would require companies to provide significantly expanded climate-related disclosures in their periodic reporting, which may require us to incur significant additional costs to comply, including the implementation of significant additional internal controls processes and procedures regarding matters that have not been subject to such controls in the past, and impose increased oversight obligations on our management and board of directors. These and other changes in stakeholder expectations will likely lead to increased costs as well as scrutiny that could heighten all of the risks identified in this risk factor. Additionally, many of our customers and suppliers may be subject to similar expectations, which may augment or create additional risks, including risks that may not be known to us.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain adequate U.S. and foreign patent protection for our product candidates, including our current product candidates, and any future product candidates we may develop, and/or our vector platform, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technologies similar or identical to ours, and our ability to successfully commercialize our current product candidates, any future product candidates we may develop, and our platform technologies may be adversely affected.

Our success depends, in large part, on our ability to obtain and maintain patent protection in the United States and other countries with respect to our current product candidates, and additional product candidates in our pipeline, and current and future innovations related to our vector platform. The patent prosecution process is expensive, time-consuming and complex; we may not be able to file, prosecute, maintain, and/or enforce all necessary or desirable patent applications and issued patents at a reasonable cost or in a timely manner. We currently have seven issued patents in the United States: (1) U.S. Patent No. 9,877,990, covering, in part, pharmaceutical formulations comprising our lead clinical product B-VEC, as well as methods of its use for treating wounds, disorders, and diseases of the skin, which we refer to as the '990 patent; (2) U.S. Patent No. 10,155,016 covering pharmaceutical compositions containing B-VEC formulated for myriad routes of administration; (3) U.S. Patent No. 10,441,614 covering aspects of our vector platform technology, and its uses in delivering any gene of interest to the skin; (4) U.S. Patent No. 10,525,090, covering pharmaceutical compositions comprising our clinical product candidate, KB105, and methods of its use for treating TGM1-deficient autosomal recessive congenital ichthyosis; (5) U.S. Patent No. 10,786,438 covering pharmaceutical compositions comprising vectors encoding cosmetic proteins, including our product candidate, KB301, and methods of its use for improving skin condition, quality, and/or appearance; (6) U.S. Patent No. 10,829,529 covering methods of using KB407 for the treatment of cystic fibrosis and other diseases causing progressive lung destruction; and (7) U.S. Patent No. 11,185,564 covering aspects of our vector platform technology, and its uses in delivering any gene of interest to the skin. Furthermore, we have nine international patent applications filed in accordance with the Paris Cooperation treaty directed to multiple discovery, preclinical, and clinical programs, including B-VEC, KB105, KB301, KB104, and KB407, as well as multiple patent applications filed in foreign jurisdictions stemming from these international applications. B-VEC is also the subject of patents granted in Australia, Europe, Japan, Mexico, New Zealand, and Singapore including European Patent No. 3 377 637 B1, covering pharmaceutical compositions containing B-VEC as well as uses thereof.

Even if we are granted the patents we are currently pursuing, they may not issue in a form that will provide us with the full scope of protection we desire, they may not prevent competitors or other third parties from competing with us, and/or they may not otherwise provide us with a competitive advantage. Our competitors, or other third parties, may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. For example, there is no assurance that the '990 patent or any other patent we are granted will prevent third parties from developing competing technologies. Moreover, our patent estate does not preclude third parties from having intellectual property rights that could interfere with our freedom to use our platform, including for dermatological or pulmonary indications. Even assuming patents issue from our pending and future patent applications, changes in either the patent laws or interpretation of the patent laws in the United States and foreign jurisdictions may diminish the value of our patents or narrow their scope of protection.

We also may not be aware of all third-party intellectual property rights potentially relating to technologies similar to our own. Publications of discoveries in the scientific literature often lag their actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after earliest priority date or, in some cases, not at all until patents are issued. Therefore, it is impossible to be certain that we were the first to develop the specific technologies as claimed in any owned patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

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

Filing, prosecuting and defending patents on each and every one of our product candidates, and current and future innovations related to our vector platform, in all countries throughout the world would be prohibitively expensive, and intellectual property rights in some countries outside the United States may differ in scope from those eventually granted in the United States. Thus, in some cases, we may not have the opportunity to obtain patent protection for certain technologies in some jurisdictions outside the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we do pursue patent protection. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products. Such challenges in enforcing rights in these countries could make it difficult for us to stop the infringement of our patents, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our current and future patent rights in foreign jurisdictions could result in substantial costs and may divert our efforts and attention from other aspects of our business; could put our patents at risk of being invalidated or interpreted narrowly; could put any future patent applications, including continuation and divisional applications, at risk of not issuing; and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce any intellectual property rights around the world stemming from intellectual property that we develop may be inadequate to obtain a significant commercial advantage in these foreign jurisdictions.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability (and the ability of any potential future collaborators) to develop, manufacture, market and sell our product candidates, and to freely use our proprietary technologies (e.g., without infringing the rights and intellectual property of others). Many companies and institutions have filed, and continue to file, patent applications related to various aspects of gene therapy. Because patent applications can take many years to issue, may be confidential for 18 months or more after filing, and can be revised before issuance, there may be applications now pending which may later result in issued patents that a third-party asserts are infringed by the manufacture, use, sale, or importation of our products. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates or related technologies, including, for example, interference proceedings, post grant review challenges, and inter partes review before the USPTO. Our competitors or other third parties may assert infringement claims against us, alleging that our therapeutics, manufacturing methods, formulations or administration methods are covered by their patents. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue, and against whom our patent portfolio may therefore have no deterrent effect.

There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patents or other intellectual property rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and adversely affect our ability to commercialize our products. 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. In such a hypothetical situation, there is no assurance that a court of competent jurisdiction would find that our product candidates or technologies do not infringe a third-party patent.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcomes are uncertain. If we are found, or believe there is a risk that we may be found, to infringe a third-party's valid and enforceable intellectual property rights, we could be required (or may choose) to obtain a license from such a third-party to continue developing, manufacturing and marketing our technologies. However, we may not be able to obtain any required license on commercially reasonable terms, if 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 further, it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technologies. We also could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing our technologies or force us to cease some or all our business operations. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time consuming. Competitors may infringe our current or future patents, should such patents issue, or we may be required to defend against claims of infringement or other unauthorized use of intellectual property. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our scientific and management personnel from their normal responsibilities. 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, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities.

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

We have been subject to claims asserting that we, our employees or our advisors have wrongfully used or disclosed alleged trade secrets of other parties or claims asserting ownership of what we regard as our own intellectual property and we may face other such claims in the future.

Certain of our employees or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including potential competitors, and we have and may in the future enter into agreements providing us with rights to intellectual property of third parties for limited purposes. Although we try to observe the terms of agreements under which we obtain access to third-party intellectual property and to ensure that our employees and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals, or we, have used or disclosed intellectual property, including trade secrets or other proprietary information, of third parties or the current or former employers of employees or advisors. If we fail in defending any such claims, in addition to paying monetary damages, we may be subject to an injunction and may lose valuable intellectual property rights or personnel. Moreover, any such litigation, or the threat thereof, may adversely affect our ability to hire new employees or contract with independent contractors. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our products, which would have an adverse effect on our business, results of operations, and financial condition. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

While it is our policy to require our employees and contractors who may be involved in the conception of intellectual property to execute agreements assigning such intellectual property rights to us, unforeseen complications may arise when fully and adequately executing such an agreement with each party who, in fact, conceives of intellectual property that we regard as our own. Examples of such complications may include, for example, when we obtain agreements assigning intellectual property to us, the assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached. Such complications may lead to us being forced to bring claims against third parties or current and former employees, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Moreover, individuals executing agreements with us may have preexisting or competing obligations to a third-party, such as an academic institution, and thus an agreement with us may be insufficient in fully perfecting ownership of inventions developed by that individual. Disputes about the ownership of intellectual property that we may own may have a material adverse effect on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. For example, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act included several significant changes to U.S. patent law, including provisions that affected the way patent applications are prosecuted, and altered strategies regarding patent litigation. These provisions also switched the United States from a "first-to-invent" system to a "first-to-file" system, allowed third-party submissions of prior art to the USPTO during patent prosecution, and set forth additional procedures to attack the validity of a patent through various post grant proceedings administered by the USPTO. As patent reform legislation can inject serious uncertainty into the patent prosecution and litigation processes, it is not clear what impact future patent reform legislation will have on the operation of our business. However, such future legislation, and its implementation, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Moreover, the patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain given the ever evolving and constantly shifting nature of precedential patent cases decided by both the U.S. Court of Appeals for the Federal Circuit and the U.S. Supreme Court. We cannot assure you that our efforts to seek patent protection for our technology and product candidates will not be negatively impacted by the future court decisions or changes in guidance or procedures issued by the USPTO. These decisions, and any guidance issued by the USPTO (or changes thereto), could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property rights in the future.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

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

Intellectual property rights and regulatory exclusivity rights do not necessarily address all potential threats.

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

- others may be able to make gene therapy products that are similar to our product candidates but that are not covered by the claims of our current patents, or of patents that we may own or license in the future;
- we, or any future license partners or collaborators, might not have been the first to file patent applications covering certain aspects of the concerned technologies;

- others may independently develop similar or alternative technologies, or duplicate any of our technologies, potentially without falling within the scope of our current or future issued claims, thus not infringing our intellectual property rights;
- it is possible that our filed or future patent applications will not lead to issued patents;
- issued patents to which we currently hold rights or to which we may hold rights in the future may be held invalid or unenforceable, including as a result of legal challenges by third parties or our competitors;
- others may have access to any future intellectual property rights licensed to us on a non-exclusive basis;
- our competitors might conduct research and development activities in countries where we do not have or pursue 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 or other intellectual property rights of others may have an adverse effect on our business; and
- we may choose not to file a patent application covering certain of our 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 significantly harm our business, financial condition, results of operations and prospects.

Risks Related to Ownership of Our Common Stock

Our Chief Executive Officer and Chairman of the Board of Directors and our founder, President, Research & Development and director will have the ability to substantially influence all matters submitted to stockholders for approval.

As of December 31, 2022, Krish S. Krishnan and Suma M. Krishnan, our Chief Executive Officer and Chairman of the Board and our founder, President, Research & Development and director, respectively, in the aggregate, beneficially owned shares representing approximately 15% of our capital stock. As a result, they will be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons would substantially influence the election of directors and approval of any merger, consolidation or sale of all or substantially all our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire or result in management of our company that our public stockholders disagree with.

If securities analysts publish negative evaluations of our stock, the price of our stock could decline.

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

Raising additional capital could cause the price of our common stock to decline and cause dilution to our stockholders, restrict our operations or require us to relinquish rights.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of private and public equity offerings, debt financings, collaborations, strategic alliances, and licensing arrangements. We may issue additional common stock or restricted securities as part of such financing activities and any such issuances may have a dilutive effect on our then-existing stockholders. Sales of substantial amounts of our common stock in the open market, or the availability of such shares for sale, could adversely affect the price of our common stock.

The incurrence of indebtedness would result in increased fixed payment obligations and a portion of our operating cash flows, if any, being dedicated to the payment of principal and interest on such indebtedness, and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business.

If we are unable to raise additional funds through equity or debt financings when needed, and instead raise additional capital through marketing and distribution agreements or other collaborations, strategic alliances, or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our current and future product candidates, technologies, future revenue streams or discovery programs or grant licenses on terms that may not be favorable to us.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for holders of our common stock.

The price of our common stock has been and is likely to continue to be volatile. The stock market in general and the market for biopharmaceutical or pharmaceutical companies specifically has experienced extreme volatility that has often been unrelated to the operating performance of such companies. As a result of this volatility, you may not be able to sell your common stock at or above the price that you paid for it. The market price of our common stock may be influenced by many factors, including:

- our ability to successfully proceed to and conduct clinical trials;
- results of clinical trials of our product candidates or those of our competitors;
- our ability to obtain regulatory approval for our product candidates and our ability to successfully commercialize any of our approved product candidates;
- the success of competitive products or technologies;
- commencement or termination of collaborations;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- our inability to manufacture adequate product supply for any approved product or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

If we fail to maintain effective internal control over financial reporting, we may not be able to accurately report our financial results, which may adversely affect investor confidence in our company and, as a result, the value of our common stock.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting and is required to have an independent auditor assess the effectiveness of our internal control over financial reporting, pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, as amended (the “Sarbanes-Oxley Act”). We cannot give any assurances that material weaknesses will not be identified in the future in connection with our compliance with the provisions of Section 404 of the Sarbanes-Oxley Act. The existence of any material weakness would preclude a conclusion by management and our independent auditors that we maintained effective internal control over financial reporting. Our management may be required to devote significant time and expense to remediate any material weaknesses that may be discovered and may not be able to remediate any material weakness in a timely manner. The existence of any material weakness in our internal control over financial reporting could also result in errors in our financial statements that could require us to restate our financial statements, cause us to fail to meet our reporting obligations and cause investors to lose confidence in our reported financial information, all of which could lead to a decline in the per-share trading price of our common stock.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so-called "poison pill," that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 80% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

We have broad discretion in the use of our cash, cash equivalents and marketable securities and may not use them effectively.

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

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Issuing additional shares of our common stock could cause the price of our common stock to decline and cause dilution to our stockholders.

As of December 31, 2022, we had 25.8 million shares of common stock issued and outstanding, and 80.0 million shares authorized for issuance. As of December 31, 2022, we also had outstanding options to purchase 3.6 million shares of common stock with a weighted-average exercise price of $61.50 per share. Outstanding vested options are likely to be exercised if the market price of our common stock exceeds the applicable exercise price. As of December 31, 2022, we had 66,600 non-vested restricted stock awards ("RSAs") at a weighted-average price of $78.89. We expect to issue additional equity awards to

directors and employees. The issuance of restricted common stock or common stock upon exercise of any outstanding options would be dilutive, and may cause the market price for a share of our common stock to decline.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

As of December 31, 2022, we lease approximately 54,000 square feet of combined laboratory and office space in Pittsburgh, Pennsylvania that we use for our research, development and manufacturing efforts. The lease for approximately 7,000 square feet of office space expires in September 2023, and the lease covering the remaining combined laboratory and office space expires in October 2031.

As of December 31, 2022, we also lease additional U.S. office space in Boston, Massachusetts and European office space in Zug, Switzerland, and Amsterdam, Netherlands.

In December 2019, we entered into a lease agreement for our second commercial gene therapy facility ("ASTRA") in the Pittsburgh, Pennsylvania area, which contained an option to purchase the building. In January 2021, we entered into a Purchase and Sale Agreement (“PSA”) with Northfield I, LLC, an Ohio limited liability company to acquire ASTRA, and the related purchase closed in March 2021. In June 2021, we entered into a Standard Form of Contract for Construction and the corresponding General Conditions of the Contract for Construction with The Whiting-Turner Contracting Company (“Whiting-Turner”), pursuant to which Whiting-Turner is constructing and managing the construction of ASTRA. The facility is under construction and expected to be completed and validated in 2023. Refer to Note 7 of the Notes to the Consolidated Financial Statements included in Part II of Item 8 of this Annual Report on Form 10-K for more information regarding this transaction.

Item 3. Legal Proceedings.

The information set forth in Note 6 of the Notes to the Consolidated Financial Statements included in Part II Item 8 of this Annual Report on Form 10-K is incorporated by reference into this Item 3.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock has been listed on the Nasdaq Capital Market under the symbol "KRYS" since September 2017. Prior to that, there was no public market for our common stock.

On February 20, 2023, there were two stockholders of record of our common stock. We are unable to estimate the total number of stockholders represented by these record holders, as many of our shares are held by brokers and other institutions on behalf of our stockholders. The closing price of our common stock was $78.25 per share as of February 20, 2023 as reported on the Nasdaq Capital Market.

Dividend Policy

We have never declared or paid cash dividends on our capital stock. We currently intend to retain any future earnings for use in the operation and growth of our business and do not intend to declare or pay any cash dividends in the foreseeable future. Any further determination to pay dividends on our capital stock will be at the discretion of our board of directors, subject to applicable laws, and will depend on our financial condition, results of operations, capital requirements, general business conditions and other factors that our board of directors considers relevant.

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

There were no repurchases of shares of common stock made during the three months ended December 31, 2022.

Sales of Unregistered Securities

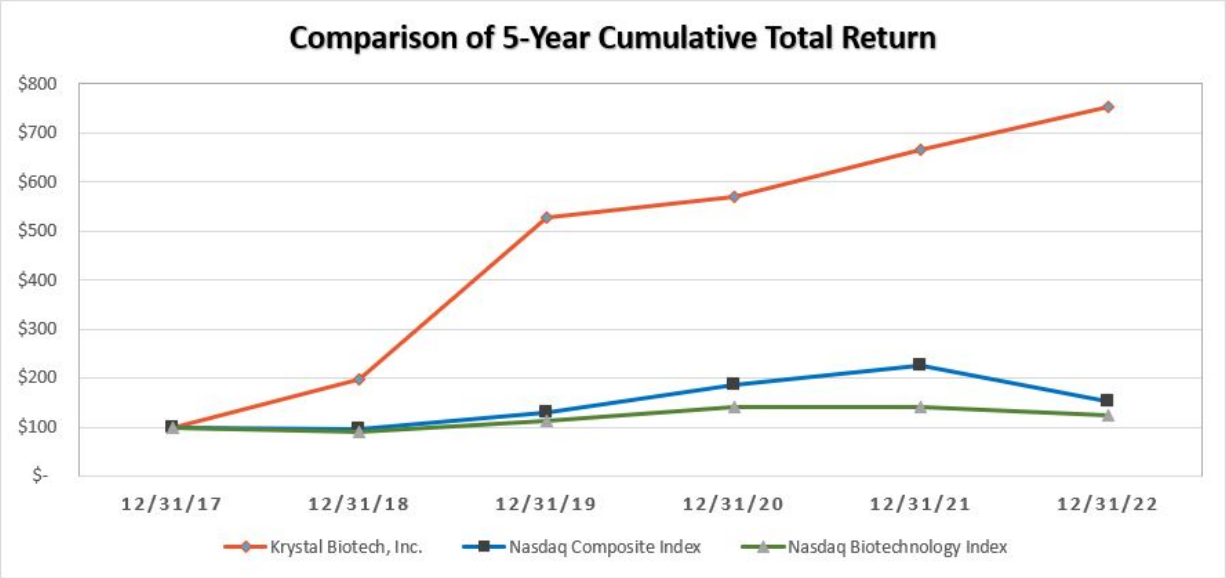
There were no sales of unregistered securities by us during the last three calendar years.

Stock Performance Graph

Set forth below is a graph comparing the cumulative total return on an indexed basis of a $100 investment in the Company's common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index commencing on December 31, 2017 and continuing through December 31, 2022. The graph assumes our closing sale price on December 31, 2017 of $10.52 per share as the initial value of our common stock for indexing purposes. Points on the graph represent the performance as of the last business day of each of the months indicated.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common stock.

This performance graph shall not be deemed "soliciting material" or to be "filed" with the SEC for purposes of Section 18 of the Exchange Act or incorporated by reference into any filing of Krystal Biotech, Inc. under the Securities Act or the Exchange Act, except to the extent we specifically incorporate it by reference into such filing. The past performance of our common stock is no indication of future performance.



Item 6. [Reserved]

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

The following information should be read in conjunction with the consolidated financial statements and related notes thereto included in this Annual Report on Form 10-K. In addition to historical information, this report contains forward-looking statements that involve risks and uncertainties which may cause our actual results to differ materially from plans and results discussed in forward-looking statements. We encourage you to review the risks and uncertainties discussed in the sections entitled Item 1A. "Risk Factors" and "Forward-Looking Statements" included at the beginning of this Annual Report on Form 10-K. The risks and uncertainties can cause actual results to differ significantly from those forecast in forward-looking statements or implied in historical results and trends. We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

This section of this Form 10-K generally discusses 2022, 2021 and 2020 items and year-to-year comparisons between 2022 and 2021, and 2021 and 2020 of the Company's results of operations and cash flows.

Overview

We are a biotechnology company focused on developing and commercializing genetic medicines for patients with rare diseases. Using our patented platform that is based on engineered HSV-1, we create vectors that efficiently deliver therapeutic transgenes to cells of interest in multiple organ systems. The cell's own machinery then transcribes and translates the encoded effector to treat or prevent disease. We formulate our vectors for non-invasive or minimally invasive routes of administration at a healthcare professional's office or potentially in the patient's home by a healthcare professional. Our goal is to develop easy-to-use medicines to dramatically improve the lives of patients living with rare diseases and chronic conditions. Our innovative technology platform is supported by in-house, commercial scale CGMP manufacturing capabilities. Refer to *Part I, Item 1 - Business* for more information about our clinical development pipeline and research programs and the status of our product candidates.

Pipeline Highlights and Recent Developments:

- B-VEC is a topical gel containing our novel vector designed to deliver two copies of the *COL7A1* transgene for the treatment of DEB, a serious rare skin disease caused by missing or mutated COL7 protein. We submitted a BLA to the FDA for B-VEC for the treatment of DEB in June 2022. The FDA accepted the BLA in August 2022 granting B-VEC a Priority Review Designation with a PDUFA action date of February 17, 2023. In January 2023, the FDA notified us, that based on manufacturing information submitted to the Agency on December 20, 2022 in response to an information request from the FDA, the PDUFA date has been revised to May 19, 2023. In this notification, we were also informed that there will be no Advisory Committee meeting for B-VEC and a REMS program is not needed for the B-VEC application. Commercial readiness efforts have been underway for the past two years as we prepare for the potential approval of B-VEC by the FDA and the EMA. In the United States our Medical Science Liaisons have been interacting with and educating HCPs on DEB and the importance of genetic testing in ensuring an accurate diagnosis. We have completed the build of Krystal Connect, our US in-house patient services call center staffed with Krystal employees, and are ready, pending FDA approval of B-VEC, to assist patients, care givers and HCPs interested in accessing B-VEC. Additionally, we have hired, trained and deployed commercial field teams who are interacting with physicians, patients, commercial payers across the U.S. to educate on DEB and to prepare for a U.S. launch of B-VEC. We are interacting frequently with the leading physicians in the major markets across Europe and in Japan.
- We submitted a request for MAA with the EMA in November 2022 for B-VEC for the treatment of DEB in patients 6 months and older. The Company was informed by the EMA in January 2023 to modify the PIP waiver request to include patients between birth and 6 months. The Company is modifying the application so that the MAA procedure can officially start in the second half of 2023 with an approval expected in early 2024.
- KB105 is a topical gel containing our novel vector designed to deliver two copies of the *TGM1* transgene for the treatment of TGM1-ARCI, a serious rare skin disorder caused by missing or mutated TGM1 protein. A randomized, placebo-controlled Phase 1/2 study is ongoing. On July 1, 2021, we announced complete data from the Phase 1 trial, showing repeat topical KB105 dosing continued to be well tolerated with no adverse events or evidence of immune response. Details of the Phase 1/2 study can be found at www.clinicaltrials.gov under NCT identifier NCT04047732.

Nothing included on this website shall be deemed incorporated by reference into this Annual Report on Form 10-K. We plan to initiate a Phase 2 study in 1H 2023.

- KB104 is a topical gel formulation of our novel vector designed to deliver two copies of the *SPINK5* transgene for the treatment of Netherton Syndrome, a debilitating autosomal recessive skin disorder caused by missing or mutated SPINK5 protein. The FDA has granted KB104 rare pediatric designation for the treatment of Netherton Syndrome. We plan to file an IND and initiate a clinical trial of KB104 to treat patients with Netherton Syndrome in 2023.
- KB407 is an inhaled (nebulized) formulation of our novel vector designed to deliver two copies of the full-length CFTR transgene for the treatment of cystic fibrosis, a serious rare lung disease caused by missing or mutated CFTR protein. On September 29, 2021, we announced that the Bellberry Human Research Ethics Committee in Australia granted approval to conduct a Phase 1 clinical study of inhaled KB407 in patients with cystic fibrosis, and trial initiation is anticipated in first half of 2023. In August 2022, we announced that the FDA had accepted our IND application to evaluate KB407 in a clinical trial to treat patients with cystic fibrosis. We are closely working with Therapeutics Development Network ("TDN") of the Cystic Fibrosis Foundation ("CFF") to validate our Phase 1 clinical protocol and plan on initiating a Phase 1 clinical trial in the US in first half of 2023.
- KB408 is an inhaled (nebulized) formulation of our novel vector designed to deliver two copies of the *SERPINA1* transgene, that encodes for normal human alpha-1 antitrypsin protein, for the treatment of alpha-1 antitrypsin deficiency ("AATD"). We presented preclinical pharmacology data for KB408 at the European Society of Gene & Cell Therapy Virtual Congress that was held October 19-22, 2021. We are planning to file an IND for KB408 to treat AATD patients in 2023.
- KB301 is a solution formulation of our novel vector for intradermal injection designed to deliver two copies of the *COL3A1* transgene to address signs of aging or damaged skin caused by declining levels of, or damaged proteins within the extracellular matrix, including type III collagen. We initiated a Phase 1 clinical trial, the PEARL-1 trial, for the treatment of aesthetic skin conditions on August 25, 2020. The Phase 1 dose-ranging trial evaluated the safety, tolerability, and initial efficacy of intradermal injections of KB301 in adult subjects aged 18-75. Details of the Phase 1 study can be found at www.clinicaltrials.gov under NCT identifier (NCT04540900). Nothing included on this website shall be deemed incorporated by reference into this Annual Report on Form 10-K. Complete results from Cohort 1 focused on safety were presented at the 2021 SID Annual Meeting. In March 2022, we announced positive proof-of-concept efficacy and safety data from Cohort 2 of the PEARL-1 study of KB301 for the treatment of aesthetic skin indications. Cohort 2 is a randomized, double-blind, placebo-controlled clinical trial that evaluated the safety and efficacy of KB301 for the improvement of fine lines and skin texture in the lower and upper cheek and for improvement in skin thickness in the knee. Cohort 2 enrolled 27 subjects across two trial sites. Bilateral treatment areas included the neck behind the ear to assess initial safety and on the cheek below and above the zygomatic arch (lower and upper cheek), and around the knee. Subjects were randomized 2:1 to receive low dose KB301 or placebo in the upper cheek and knee as multiple micro depot injections over the selected treatment area with a 33 G needle. Subjects receiving KB301 in the lower check were randomized 2:1 to receive either low dose KB301, high dose KB301 or placebo. Four patients dropped out of the Cohort 2 study – one subject following the initial safety assessment behind the ear, two subjects for unspecified reasons, and one subject due to unevenness in face between active and placebo during the study. A subset of subjects from the PEARL-1 Cohort 2 trial (Cohort 3) were enrolled into a durability trial to look for duration of effect, reduction of the unevenness in placebo treated sites, and for long term safety monitoring. Ten subjects from the PEARL-1 Cohort 2 study were enrolled in durability trial, an open-label study to assess duration of effect below the zygomatic arch (the lower cheek area). The extension cohort enrolled subjects who had received the high dose regimen of KB301 during the efficacy cohort in one or both of their lower cheeks. Subject Satisfaction Scores and Investigator Assessments were measured monthly for three consecutive visits that correspond to timepoints up to nine-months following administration of the last dose of KB301. In addition, subjects with placebo-treated lower cheeks were dosed with KB301 during the open-label extension cohort to normalize their appearance. In November 2022, we announced nine-month durability of effect in Cohort 3 of the PEARL-1 study of KB301. We are planning to initiate a Phase 2 study in fine lines in 2023.

Jeune Aesthetics has several other aesthetic medicine product candidates in various stages of preclinical development reflected in the chart above in *Item 1- Business*.

Business Highlights:

- In March 2022, we presented additional results from our Phase 3 study of the clinical efficacy and safety of B-VEC for the treatment of DEB at the 2022 American Academy of Dermatology Annual Meeting.
- In March 2022, results from the complete Phase 1/2 study of topical B-VEC for the treatment of DEB were published in *Nature Medicine.*

- On April 5, 2022, the Company issued and sold 434,782 shares of common stock at a weighted average price of $69.00 per share for net proceeds of $29.1 million after deducting selling commissions of approximately $900 thousand.
- On April 28, 2022, the Company entered into a final settlement agreement with PeriphaGen, Inc. ("PeriphaGen") to resolve all claims in the trade secret litigation filed by PeriphaGen in May 2020. We paid PeriphaGen an upfront payment of $25.0 million for: (i) the release of all claims in the trade secret litigation with PeriphaGen; (ii) the acquisition of certain PeriphaGen assets, and (iii) the grant of a license by PeriphaGen for dermatological applications. Upon approval of the Company's first product by the FDA, the Company will pay PeriphaGen an additional $12.5 million, followed by three additional $12.5 million contingent milestone payments upon reaching $100.0 million in total cumulative sales, $200.0 million in total cumulative sales and $300.0 million in total cumulative sales.
- In April 2022, following feedback from the FDA, we announced that we planned to offer patients with DEB, who were enrolled in the GEM-3 OLE, the opportunity to be dosed in their homes by a health care professional.
- In April 2022, Jeune Aesthetics announced the formation and members of its Scientific Advisory Board, comprised of industry leaders to serve as strategic advisors assisting with program strategy and clinical development.
- In May 2022, we presented new data entitled "GEM-3: phase 3 safety and immunogenicity results of Beremagene Geperpavec ("B-VEC"), an investigational, topical gene therapy for dystrophic epidermolysis bullosa (DEB)" at the SID 2022 Annual Meeting.
- In December 2022 full results from the GEM-3 trial of B-VEC for DEB were published in the *New England Journal of Medicine*.

COVID-19 Update

To date the impact of the COVID-19 pandemic on our business and clinical trials in the U.S. has been minimal. We will continue to assess the potential impact of the pandemic on our business and operations, including our supply chain and preclinical and clinical trial activities. Outside of the U.S., we have experienced pandemic-related delays in clinical trial initiation in Australia, and we will continue to closely monitor the impact that future pandemic developments have on this and our other clinical trials, going forward. For additional information regarding the impact of the coronavirus pandemic, please see "Risk Factors - Business interruptions resulting from the COVID-19 outbreak or similar public health crises could cause a disruption of the development efforts of our product candidates and adversely impact our business."

Financial Overview

Revenue

We currently have no approved products for commercial marketing or sale and have not generated any revenue from the sale of products or other sources to date. In the future, we may generate revenue from product sales, royalties on product sales, or license fees, milestones, or other upfront payments if we enter into any collaborations or license agreements. We expect that our future revenue will fluctuate from quarter to quarter for many reasons, including the uncertain timing and amount of any such sales.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred to advance our preclinical and clinical candidates, which include:

- expenses incurred under agreements with contract manufacturing organizations ("CMOs"), consultants and other vendors that conduct our preclinical activities;
- costs of acquiring, developing and manufacturing clinical trial materials and lab supplies;
- facility costs, depreciation and other expenses, which include direct expenses for rent and maintenance of facilities and other supplies; and
- payroll related expenses, including stock-based compensation expense.

We expense internal research and development costs to operations as incurred. We expense third-party costs for research and development activities, such as the manufacturing of preclinical and clinical materials, based on an evaluation of the progress to completion of specific tasks such as manufacturing of drug substance, fill/finish and stability testing, which is

provided to us by our vendors. We expect our research and development expenses will increase as we continue the manufacturing of preclinical and clinical materials and manage the clinical trials of, and seek regulatory approval for, our product candidates and expand our product portfolio. In the near term, we expect that our research and development expenses will increase as we continue our open label extension study for B-VEC, resume dosing with KB105 Phase 1/2 clinical trial, initiate a Phase 2 trial for KB301, initiate Phase 1 trials for KB407, initiate a Phase 1 trial for KB104, and incur preclinical expenses for our other product candidates. Due to the numerous risks and uncertainties associated with product development, we cannot determine with certainty the duration, costs and timing of clinical trials, and, as a result, the actual costs to complete clinical trials may exceed the expected costs.

General and Administrative Expenses

General and administrative expenses consist principally of salaries and other related costs, including stock-based compensation, for personnel in our executive, commercial, business development and other administrative functions. General and administrative expenses also include professional fees associated with corporate and intellectual property related legal expenses, consulting and accounting services, facility-related costs and expenses associated with obtaining and maintaining patents. Other general and administrative costs include travel expenses.

We anticipate that our general and administrative expenses will increase in the future to support the continued research and development of our product candidates. These increases will likely include increased costs for insurance, costs related to the hiring of additional personnel and payments to outside consultants, lawyers and accountants, among other expenses. Additionally, we anticipate that we will continue to increase our salary and personnel costs and other expenses as a result of our preparation for commercial operations.

ASTRA Capital Expenditures

In March 2021, we closed on the purchase of the building that was constructed to house our second CGMP facility, ASTRA. We are currently in the process of constructing the interior build-out of this facility and we have entered into a contract with Whiting-Turner who manages the construction of ASTRA. Further, we have entered into various non-cancellable purchase agreements for long-lead materials to help avoid potential schedule disruptions or material shortages. These contracts typically call for the payment of fees for services or materials upon the achievement of certain milestones. We expect to continue to incur significant capital expenditures related to ASTRA as we construct and validate the facility, which is expected to be completed in 2023.

Interest Income

Interest income consists primarily of income earned from our cash, cash equivalents and investments.

Interest Expense

Interest expense consists primarily of non-cash interest expense recognized to accrete the build to suit financial obligation to a balance that equaled the cash consideration that was paid upon the close of the purchase of ASTRA.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial position and results of operations is based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or GAAP. The preparation of financial statements in conformity with GAAP requires us to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, we evaluate estimates which include, but are not limited to, estimates related to clinical trial and contract manufacturing prepayments and accruals, stock-based compensation expense, accrued expenses, the fair value of financial instruments, the incremental borrowing rate for lease liabilities, and the valuation allowance included in the deferred income tax calculation during the period. We base our estimates on historical experience and other market-specific or other relevant assumptions that we believe to be reasonable under the circumstances. Actual results may differ materially from those estimates or assumptions.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses, prepaid assets and other current liabilities. This process involves reviewing open contracts and

commitments, communicating with our personnel to identify services that have been performed for us and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued research and development expenses, prepaid assets and other current liabilities as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of accrued research and development expenses, prepaid assets and other current liabilities include fees paid to contract manufacturers made in connection with the manufacturing of preclinical and clinical trials materials.

We base our expenses related to clinical manufacturing on our estimates of the services performed pursuant to contracts with the entities producing clinical materials 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. Payments under these types of contracts depend heavily upon the successful completion of many separate tasks involved in the manufacturing of drug product. In accruing service fees, we estimate the time period over which services will be performed, and the actual services performed in each period. If our estimates of the status and timing of services performed differs from the actual status and timing of services performed we may report amounts that are too high or too low in any particular period. To date, there have been no material differences from our estimates to the amount actually incurred.

Stock-Based Compensation

We have applied the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification, or ASC, Topic 718, *Compensation—Stock Compensation* ("ASC 718"), to account for stock-based compensation. We recognize compensation costs related to stock options granted based on the estimated fair value of the awards on the date of grant. Described below is the methodology we have utilized in measuring stock-based compensation expense.

ASC 718 requires all stock-based payments, including grants of stock options and restricted stock, to be recognized in the statements of operations based on their grant-date fair values. Compensation expense is recognized on a straight-line basis based on the grant-date fair value over the associated service period of the award, which is generally the vesting term.

Determining the amount of stock-based compensation to be recorded requires us to develop estimates of the fair value of stock-based awards as of their measurement date. We recognize stock-based compensation expense over the requisite service period, which is the vesting period of the award. Calculating the fair value of stock-based awards requires that we make assumptions. We use the Black-Scholes option pricing model to value our stock option awards. Use of this valuation methodology requires that we make assumptions as to the volatility of our common stock, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Once our own sufficient historical volatility data was obtained, we eliminated the use of a representative peer group and as of Q4 2021 we use only our own historical volatility data in its estimate of expected volatility given that there is now sufficient amount of historical information regarding the volatility of our own stock price. We use the simplified method to calculate the expected term as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment* as we do not have sufficient historical stock option activity data to provide a reasonable basis upon which to estimate the expected term of stock options granted to employees. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention of paying cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life.

Leases

We account for our lease agreements in accordance with Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 842, *Leases* ("ASC 842"). As our lease agreements do not provide an implicit rate and as we do not have external borrowings, we use an estimated incremental borrowing rate based on the information available at lease commencement in determining the present value of lease payments. The incremental borrowing rate is the rate of interest that we would expect to borrow on a collateralized and fully amortizing basis over a similar term an amount equal to the lease payments in a similar economic environment.

For lease arrangements where it has been determined that we have control over an asset that is under construction and is thus considered the accounting owner of the asset during the construction period, we record a construction-in-progress asset ("CIP") and corresponding financial obligation on the consolidated balance sheet. Once the construction is complete, an assessment will be performed to determine whether the lease meets certain "sale-leaseback" criteria. If the sale-leaseback criteria are determined to be met, we will remove the asset and related financial obligation from the balance sheet and treat the building lease as either an operating or finance lease based on our assessment of the guidance. If, upon completion of construction, the project does not meet the "sale-leaseback" criteria, the lease will be treated as a financing obligation and we will depreciate the asset over its estimated useful life for financial reporting purposes.

Results of Operations

Years Ended December 31, 2022, 2021 and 2020

(in thousands)	Years Ended December 31, 2022	2021	2020	Change 2022 vs. 2021	2021 vs. 2020
Expenses					
Research and development	$ 42,461	$ 27,884	$ 17,936	$ 14,577	$ 9,948
General and administrative	77,735	40,391	15,063	37,344	25,328
Litigation settlement	25,000	—	—	25,000	—
Total operating expenses	145,196	68,275	32,999	76,921	35,276
Loss from operations	(145,196)	(68,275)	(32,999)	(76,921)	(35,276)
Other Expense					
Interest and other income, net	5,221	197	832	5,024	(635)
Interest expense	—	(1,492)	—	1,492	(1,492)
Total interest and other income, net	5,221	(1,295)	832	6,516	(2,127)
Net loss	$ (139,975)	$ (69,570)	$ (32,167)	$ (70,405)	$ (37,403)

Research and Development Expenses

Research and development expenses increased $14.6 million for the year ended December 31, 2022 compared to the year ended December 31, 2021. Higher research and development expenses were due to increases in payroll related expenses of $8.9 million which is primarily driven by an increase in personnel to support overall growth and includes a $4.5 million increase in stock-based compensation, an increase in outsourced research and development activities of $2.3 million, an increase in preclinical, clinical and pre-commercial manufacturing activities of $1.0 million, and an increase in other research and development expenses of $2.4 million, primarily due to increases in depreciation and licensing fees.

Research and development expenses increased $9.9 million for the year ended December 31, 2021 compared to the year ended December 31, 2020. Higher research and development expenses were due to increases in preclinical, clinical and pre-commercial manufacturing activities of $3.3 million, payroll related expenses of approximately $3.1 million which is primarily driven by an increase in personnel to support overall growth and includes a $2.4 million increase in stock-based compensation, an increase in outsourced research and development activities of $2.0 million, travel related expenses associated with our clinical trial sites of $187 thousand, and other research and development expenses of $1.3 million, primarily due to depreciation and rent.

General and Administrative Expenses

General and administrative expenses increased $37.3 million for the year ended December 31, 2022 compared to the year ended December 31, 2021. Higher general and administrative spending was due largely to increased payroll related expenses of approximately $28.8 million which is primarily driven by an increase in personnel to support overall growth and includes an approximate $13.4 million increase in stock-based compensation, increased commercial preparedness expenses of approximately $5.7 million, increased medical affairs costs of $581 thousand, increased travel costs of $536 thousand, and an increase in other administrative expenses of $2.9 million, primarily due to increases in utilities, information technology costs, and conference fees. These increases were partially offset by a decrease in net legal costs of $1.2 million, which consists of a decrease in legal and professional fees of $2.8 million offset by a decrease in litigation proceeds of approximately $1.6 million, due primarily to the settlement of the PeriphaGen litigation.

General and administrative expenses increased $25.3 million for the year ended December 31, 2021 compared to the year ended December 31, 2020. Higher general and administrative spending was due largely to increased payroll related expenses of approximately $14.7 million which is primarily driven by an increase in personnel to support overall growth and includes an approximate $9.6 million increase in stock-based compensation, commercial preparedness expenses of approximately $3.8 million, legal and professional fees of approximately $3.7 million which is net of $2.1 million of insurance proceeds, software related costs of $1.0 million, medical affairs costs of $508 thousand, insurance costs of $427 thousand and other administrative expenses of $1.2 million.

Litigation settlement

We incurred litigation settlement expenses for the year ended December 31, 2022 of $25.0 million, which consisted of the settlement of litigation with PeriphaGen. See “Legal Proceedings” in Note 6 of the notes to consolidated financial statements included in this Form 10-K for more information.

Other Income (Expense)

Interest and other income for the year ended December 31, 2022, 2021, and 2020 was $5.2 million, $197 thousand and $832 thousand, respectively, and consisted of realized gains from maturities of our investments, interest, and dividend income earned from our cash, cash equivalents and investments.

Interest expense for the year ended December 31, 2022, 2021 and 2020 was zero, $1.5 million, and zero, respectively. The 2021 interest expense related to accretion of the financial obligation for the build to suit lease liability during the year ended December 31, 2021 to a balance that equaled the purchase consideration for ASTRA.

Liquidity and Capital Resources

Overview

On December 31, 2022, our cash, cash equivalents and short-term investments balance was approximately $379.2 million. Since operations began, we have incurred operating losses. Our net losses were $140.0 million, $69.6 million, and $32.2 million for the years ended December 31, 2022, 2021, and 2020 respectively. At December 31, 2022, we had an accumulated deficit of $280.8 million. With the net proceeds raised from our previous public offerings, we believe that our cash, cash equivalents and short-term investments will be sufficient to allow us to fund our operations for at least 12 months from the filing date of this Form 10-K.

As we continue to incur losses, a transition to profitability is dependent upon the successful development, approval and commercialization of our product candidates and the achievement of a level of revenues adequate to support our cost structure. Furthermore, we expect to incur increasing costs associated with satisfying regulatory and quality standards, maintaining product and clinical trials, and furthering our efforts around our current and future product candidates. We may never achieve profitability, and until we do, the Company will continue to need to raise additional capital or obtain financing from other sources.

Costs related to clinical trials can be unpredictable and therefore there can be no guarantee that we will have sufficient capital to fund our continued clinical studies of B-VEC, KB105, KB301 or our planned clinical and preclinical studies for our other product candidates, or our operations. Further, we do not expect to generate any product revenues in the first quarter of 2023, assuming we receive marketing approval for B-VEC on the schedule we currently contemplate. While we are in the process of building out our internal vector manufacturing capacity, some of our manufacturing activities will be contracted out to third parties. Additionally, we currently utilize third-party Contract Research Organizations (“CROs”) to carry out some of our clinical development activities. As we seek to obtain regulatory approval for any of our product candidates, we expect to continue to incur significant manufacturing and commercialization expenses as we prepare for product sales, marketing, commercial manufacturing, packaging, labeling and distribution. Furthermore, pursuant to our settlement agreement with PeriphaGen, we will be required to pay $12.5 million upon the approval of our first product by the FDA, followed by three additional $12.5 million contingent milestone payments upon reaching $100.0 million in total cumulative sales, $200.0 million in total cumulative sales and $300.0 million in total cumulative sales. Our funds may not be sufficient to enable us to conduct pivotal clinical trials for, seek marketing approval for or commercially launch B-VEC, KB105, KB301 or any other product candidate. Accordingly, to obtain marketing approval for and to commercialize these or any other product candidates, we may be required to obtain further funding through public or private equity offerings, debt financings, collaboration and licensing arrangements or other sources. Adequate additional financing may not be available to us on acceptable terms, if at all. Our failure to raise capital when needed could have a negative effect on our financial condition and our ability to pursue our business strategy.

Operating Capital Requirements

Our primary uses of capital are, and we expect will continue to be for the near future, compensation and related expenses, manufacturing costs for preclinical and clinical materials, third-party clinical trial research and development services, laboratory and related supplies, clinical costs, legal and other regulatory expenses, payments of settlement amounts to PeriphaGen and general overhead costs. In order to complete the process of obtaining regulatory approval for any of our product candidates and to build the sales, manufacturing, marketing and distribution infrastructure that we believe will be necessary to commercialize our product candidates, if approved, we may require substantial additional funding.

We have based our projections of operating capital requirements on assumptions that may prove to be incorrect and we may use all of our available capital resources sooner than we expect. Because of the numerous risks and uncertainties associated

with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

- the timeline and cost of our OLE study for B-VEC;
- the progress, timing and costs of our ongoing Phase 1/2 clinical trials for KB105;
- the progress, results and costs of our Phase 2 clinical trials for KB301;
- the progress, results and costs of our Phase 1 clinical trials for KB407;
- the progress, timing, and costs of manufacturing of B-VEC;
- the continued development and the filing of an IND application for future product candidates;
- the initiation, scope, progress, timing, costs and results of drug discovery, laboratory testing, manufacturing, preclinical studies and clinical trials for any other product candidates that we may pursue in the future, if any;
- the costs of maintaining our own commercial-scale CGMP manufacturing facilities;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs associated with manufacturing process development and evaluation of third-party manufacturers;
- the extent to which the costs of our product candidates, if approved, will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors;
- the costs of commercialization activities for our current and future product candidates if we receive marketing approval for such product candidates we may develop, including the costs and timing of establishing product sales, medical affairs, marketing, distribution and manufacturing capabilities;
- subject to receipt of marketing approval, if any, revenue received from commercial sale of our current and future product candidates;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish;
- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, maintenance, defense and enforcement of any patents or other intellectual property rights, including milestone and royalty payments and patent prosecution fees that we are obligated to pay pursuant to our license agreements;
- our current license agreements remaining in effect and our achievement of milestones under those agreements;
- our ability to establish and maintain collaborations and licenses on favorable terms, if at all; and
- the extent to which we acquire or in-license other product candidates and technologies.

We may need to obtain substantial additional funding in order to receive regulatory approval and to commercialize our product candidates. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, the ownership interests of our existing stockholders may be materially diluted and the terms of these securities could include liquidation or other preferences that could adversely affect the rights of our existing stockholders. In addition, debt financing, if available, would result in increased fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, that could adversely affect our ability to conduct our business. If we are unable to raise capital when needed or on attractive terms, we could be forced to significantly delay, scale back or discontinue the development or commercialization of our product candidates, seek collaborators at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available, and relinquish or license, potentially on unfavorable terms, our rights to our product candidates that we otherwise would seek to develop or commercialize ourselves.

Contractual Obligations

Operating Leases

Operating lease payments represent our commitments for future minimum rent made under non-cancelable leases for our corporate headquarters in Pittsburgh, Pennsylvania, office location in Boston, Massachusetts, office locations in Switzerland and Netherlands, and for the ground lease associated with our second CGMP manufacturing facility, ASTRA. The

total future payments for our operating lease obligations at December 31, 2022 are $17.8 million, of which $1.6 million is due in the next twelve months and the remaining payments are due over the terms of the respective leases. For additional details regarding our leases, see Note 7 to our consolidated financial statements included in this Annual Report on Form 10-K.

Clinical Supply and Product Manufacturing Agreements

We enter into various agreements in the normal course of business with CROs, CMOs and other third parties for preclinical research studies, clinical trials and testing and manufacturing services. We are obligated to make milestone payments under certain of these agreements. The estimated remaining commitment as of December 31, 2022 under these agreements is approximately $2.1 million, all of which is expected to be due in the next twelve months.

Commercial Preparedness Agreements

We have contracted with various third parties to facilitate, coordinate and perform agreed upon commercial preparedness and market research activities relating to our lead product candidate, B-VEC. These contracts typically call for the payment of fees for services upon the achievement of certain milestones. The estimated remaining commitment as of December 31, 2022 is $8.4 million, all of which is expected to be due in the next twelve months.

ASTRA Contractual Obligations

We have contracted with various third parties to construct our second CGMP facility, ASTRA. Additionally, we have entered into various non-cancellable purchase agreements for long-lead materials to help avoid potential schedule disruptions or material shortages. These contracts typically call for the payment of fees for services or materials upon the achievement of certain milestones. The estimated remaining commitment as of December 31, 2022 is $16.3 million, all of which is expected to be due in the next twelve months.

Cash Flows

The following table summarizes our sources and uses of cash (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Net cash used in operating activities	$ (100,569)	$ (47,938)	$ (26,083)
Net cash used in investing activities	(114,083)	(226,770)	(11,181)
Net cash provided by financing activities	35,347	347,685	118,019
Effect of exchange rate changes on cash and cash equivalents	(41)	—	—
Net change in cash	$ (179,346)	$ 72,977	$ 80,755

Operating Activities

Net cash used in operating activities for the year December 31, 2022 was $100.6 million and consisted primarily of a net loss of $140.0 million adjusted for non-cash items of $36.6 million primarily made up of stock-based compensation expense of $33.2 million and depreciation and amortization of $4.1 million, and cash provided by decreases in net working capital of approximately $2.8 million.

Net cash used in operating activities for the year December 31, 2021 was $47.9 million and consisted primarily of a net loss of $69.6 million adjusted for non-cash items of $19.1 million primarily made up of stock-based compensation expense of $15.3 million, depreciation and amortization of $2.8 million and build to suit interest expense of $1.5 million, and cash provided by decreases in net working capital of approximately $2.5 million.

Net cash used in operating activities for the year ended December 31, 2020 was $26.1 million and consisted primarily of a net loss of $32.2 million adjusted for non-cash items of $5.2 million primarily made up of depreciation and amortization of $1.9 million and stock-based compensation expense of $3.3 million, and cash provided by decreases in net working capital of approximately $918 thousand.

Investing Activities

Net cash used in investing activities for the year ended December 31, 2022 was approximately $114.1 million and consisted primarily of purchases of $318.8 million of available-for-sale investment securities, and expenditures of $53.0 million on the build-out of our ASTRA facility, leasehold improvement of new office space, and purchases of computer and laboratory equipment, partially offset by proceeds of $257.7 million from maturities of investments.

Net cash used in investing activities for the year ended December 31, 2021 was approximately $226.8 million and consisted primarily of purchases of $190.5 million of available-for-sale investment securities, and expenditures of $68.3 million on the build-out of our ASTRA facility, leasehold improvement of new office space, and purchases of computer and laboratory equipment, partially offset by proceeds of $32.0 million from maturities of investments.

Net cash used in investing activities for the year ended December 31, 2020 was $11.2 million and consisted primarily of purchases of $3.2 million of short-term available-for-sale investment securities, and expenditures of $14.8 million on the build-out of our ASTRA facility, leasehold improvement of new office space, and purchases of computer and laboratory equipment, partially offset by proceeds of $6.9 million from maturities of short-term investments.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022 was $35.3 million and was primarily from proceeds from public offerings of 434,782 shares of our common stock at a weighted average price of $69.00 per share through our at-the-market equity offering program ("ATM") Program. Our net proceeds from the offerings were $29.1 million after deducting underwriting discounts and commissions of approximately $900 thousand. Additionally, we received $7.0 million of proceeds related to the exercise and settlement of employee stock options and restricted stock awards, offset by $649 thousand of taxes paid for the settlement of restricted stock awards.

Net cash provided by financing activities for the year ended December 31, 2021 was $347.7 million and was primarily from proceeds from follow-on public offerings of 2,211,538 shares of its common stock, including 288,461 shares purchased by the underwriters, at $65.00 per share and 2,866,667 shares of its common stock, including 200,000 shares purchased by the underwriters, at $75.00 per share. Our net proceeds from the offerings were $336.8 million after deducting underwriting discounts and commissions of approximately $21.5 million, and other offering expenses payable of $425 thousand.

Net cash provided by financing activities for the year ended December 31, 2020 was $118.0 million and was primarily from proceeds from our public offering in May 2020 of 2,275,000 shares of our common stock to the public at $55 per share. Our net proceeds from the offering were $117.2 million after deducting underwriting and commissions of approximately $7.5 million and other offering expenses of approximately $463 thousand.

Recent Accounting Pronouncements

See note 2 to our consolidated financial statements.

Item 7A. Qualitative and Quantitative Disclosures About Market Risk

We had cash, cash equivalents and short-term investments of approximately $379.2 million as of December 31, 2022, which consist primarily of money market funds, commercial paper, corporate bonds, and government agency securities. The investments in these financial instruments are made in accordance with an investment policy which specifies the categories, allocations and ratings of securities we may consider for investment. The primary objective of our investment activities is to preserve principal while at the same time maximizing the income we receive without significantly increasing risk. Some of the financial instruments in which we invest could be subject to market risk. This means that a change in prevailing interest rates may cause the value of the instruments to fluctuate. For example, if we purchase a security that was issued with a fixed interest rate and the prevailing interest rate later rises, the value of that security will probably decline. To minimize this risk, we intend to maintain a portfolio which may include cash, cash equivalents and short-term investment securities available-for-sale in a variety of securities which may include money market funds, government and non-government debt securities and commercial paper, all with various maturity dates. Based on our current investment portfolio, we do not believe that our results of operations or our financial position would be materially affected by an immediate change of 10% in interest rates.

As of December 31, 2022, we have established operations in Europe and Australia and hold cash in Australian Dollars (“AUD”), Swiss Francs (“CHF”), and Euros (“EUR”). We are subject to foreign exchange rate risk arising from transactions conducted in the aforementioned foreign currencies, however our foreign operations are not currently material to our business. We do not believe that our results of operations or our financial position would be materially affected by an immediate change of 10% in foreign currency exchange rates.

We do not hold or issue derivatives, derivative commodity instruments or other financial instruments for speculative trading purposes. Further, we do not believe our cash, cash equivalents and short-term investments have significant risk of default or illiquidity. While we believe our cash, cash equivalents and short-term investments do not contain excessive risk, we cannot provide absolute assurance that any investments we make in the future will not be subject to adverse changes in market value. Our cash, cash equivalents and short-term investments are recorded at fair value.

Item 8. Financial Statements and Supplementary Data.

INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Krystal Biotech, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheet of Krystal Biotech, Inc. and subsidiaries (the Company) as of December 31, 2022, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for the year then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022, and the results of its operations and its cash flows for the year ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission, and our report dated February 27, 2023 expressed an unqualified opinion on the effectiveness of the Company's internal control over financial reporting.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

Critical Audit Matters

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

/s/ KPMG LLP

We have served as the Company's auditor since 2022.

Pittsburgh, Pennsylvania
February 27, 2023

Report of Independent Registered Public Accounting Firm

To the Board of Directors and
Stockholders of Krystal Biotech, Inc.:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Krystal Biotech, Inc. (the "Company") as of December 31, 2021, and the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for the years ended December 31, 2021 and 2020, 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, 2021, and the results of their operations and their cash flows for the years ended December 31, 2021 and 2020, 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. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Mayer Hoffman McCann P.C.

We have served as the Company's auditor since 2017, which ended in 2022.
San Diego, California
February 28, 2022

Krystal Biotech, Inc.
Consolidated Balance Sheets

(In thousands, except shares and par value data)	December 31, 2022	December 31, 2021
Assets		
Current assets		
Cash and cash equivalents	$ 161,900	$ 341,246
Short-term investments	217,271	96,850
Prepaid expenses and other current assets	4,608	4,171
Total current assets	383,779	442,267
Property and equipment, net	161,684	112,355
Long-term investments	4,621	64,371
Right-of-use assets	8,042	7,228
Other non-current assets	324	74
Total assets	$ 558,450	$ 626,295
Liabilities and Stockholders' Equity		
Current liabilities		
Accounts payable	$ 3,981	$ 8,398
Current portion of lease liability	1,561	1,041
Accrued expenses and other current liabilities	23,305	16,297
Total current liabilities	28,847	25,736
Lease liability	7,372	6,983
Total liabilities	36,219	32,719
Commitments and contingencies (Note 6)		
Stockholders' equity		
Common stock; $0.00001 par value; 80,000,000 shares authorized at December 31, 2022 and 2021; 25,763,743 and 25,207,985 shares issued and outstanding at December 31, 2022 and 2021, respectively	—	—
Additional paid-in capital	803,718	734,523
Accumulated other comprehensive loss	(728)	(163)
Accumulated deficit	(280,759)	(140,784)
Total stockholders' equity	522,231	593,576
Total liabilities and stockholders' equity	$ 558,450	$ 626,295

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

Krystal Biotech, Inc.
Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except share and per share data)	Year Ended December 31, 2022	2021	2020
Expenses			
Research and development	$ 42,461	$ 27,884	$ 17,936
General and administrative	77,735	40,391	15,063
Litigation settlement	25,000	—	—
Total operating expenses	145,196	68,275	32,999
Loss from operations	(145,196)	(68,275)	(32,999)
Other Income (Expense)			
Interest and other income, net	5,221	197	832
Interest expense	—	(1,492)	—
Net loss	(139,975)	(69,570)	(32,167)
Unrealized loss on available-for-sale securities and other	(565)	(169)	(4)
Comprehensive loss	$ (140,540)	$ (69,739)	$ (32,171)
Net loss per common share: Basic and diluted	$ (5.49)	$ (3.13)	$ (1.71)
Weighted-average common shares outstanding: Basic and diluted	25,491,721	22,196,846	18,787,161

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

Krystal Biotech, Inc.
Consolidated Statements of Stockholders' Equity

(In thousands, except shares)	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balances at January 1, 2020	17,354,310	$ —	$ 241,951	$ 10	$ (39,047)	$ 202,914
Issuance of common stock, net	2,359,910	—	118,035	—	—	118,035
Stock-based compensation expense	—	—	3,306	—	—	3,306
Unrealized loss on investments and other (1)	—	—	—	(4)	—	(4)
Net loss	—	—	—	—	(32,167)	(32,167)
Balances at December 31, 2020	19,714,220	$ —	$ 363,292	$ 6	$ (71,214)	$ 292,084
Issuance of common stock, net	5,493,765	—	355,628	—	—	355,628
Stock-based compensation expense	—	—	15,603	—	—	15,603
Unrealized loss on investments and other (1)	—	—	—	(169)	—	(169)
Net loss	—	—	—	—	(69,570)	(69,570)
Balances at December 31, 2021	25,207,985	$ —	$ 734,523	$ (163)	$ (140,784)	$ 593,576
Issuance of common stock, net	573,637	—	36,063	—	—	36,063
Shares surrendered for taxes and forfeitures	(17,879)	—	(649)	—	—	(649)
Stock-based compensation expense	—	—	33,781	—	—	33,781
Unrealized loss on investments and other (1)	—	—	—	(565)	—	(565)
Net loss	—	—	—	—	(139,975)	(139,975)
Balances at December 31, 2022	25,763,743	$ —	$ 803,718	$ (728)	$ (280,759)	$ 522,231

(1) Includes foreign currency translation loss of $78 thousand, gain of $7 thousand, and loss of $1 thousand for the years ended December 31, 2022, 2021, and 2020, respectively.

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

Krystal Biotech, Inc.
Consolidated Statements of Cash Flows

(In thousands)	Years Ended December 31, 2022	2021	2020
Operating Activities			
Net loss	$ (139,975)	$ (69,570)	$ (32,167)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation and amortization	4,055	2,769	1,851
Stock-based compensation expense	33,230	15,319	3,272
Loss on disposal of fixed assets	72	—	33
Non-cash interest expense	—	1,492	—
Other, net	(762)	(454)	11
Changes in operating assets and liabilities			
Prepaid expenses and other current assets	(311)	(691)	(1,922)
Other non-current assets	(150)	65	(934)
Lease liability	(647)	(285)	685
Accounts payable	(1,254)	712	783
Accrued expenses and other current liabilities	5,173	2,705	2,305
Net cash used in operating activities	(100,569)	(47,938)	(26,083)
Investing Activities			
Purchases of property and equipment	(52,979)	(68,336)	(14,843)
Purchases of investments	(318,781)	(190,462)	(3,205)
Proceeds from maturities of investments	257,677	32,028	6,867
Net cash used in investing activities	(114,083)	(226,770)	(11,181)
Financing Activities			
Proceeds from issuance of common stock, net	35,996	355,645	118,019
Taxes paid related to settlement of restricted stock awards	(649)	—	—
Repayment of ASTRA build to suit liability	—	(7,960)	—
Net cash provided by financing activities	35,347	347,685	118,019
Effect of exchange rate changes on cash and cash equivalents	(41)	—	—
Net change in cash and cash equivalents	(179,346)	72,977	80,755
Cash and cash equivalents at beginning of year	341,246	268,269	187,514
Cash and cash equivalents at end of year	$ 161,900	$ 341,246	$ 268,269
Supplemental Disclosures of Non-Cash Investing and Financing Activities			
Unpaid purchases of property and equipment	$ 14,927	$ 15,363	$ 9,697
Initial recognition of right-of-use assets	$ 1,556	$ 4,396	$ 911

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

1. Organization

Krystal Biotech, Inc. (the "Company," or "we" or other similar pronouns) commenced operations in April 2016. In March 2017, the Company converted from a California limited liability company to a Delaware C-corporation, and changed its name from Krystal Biotech LLC to Krystal Biotech, Inc. In June 2018, the Company incorporated a wholly-owned subsidiary in Australia for the purpose of undertaking preclinical and clinical studies in Australia. In April 2019, the Company incorporated Jeune Aesthetics, Inc ("Jeune Aesthetics"), in Delaware, a wholly-owned subsidiary, for the purpose of undertaking preclinical and clinical studies for aesthetic skin conditions. In January 2022, August 2022, and December 2022, the Company incorporated wholly-owned subsidiaries in Switzerland, Netherlands, and France, respectively, for the purpose of establishing initial operations in Europe for the development and commercialization of Krystal's product pipeline.

We are a biotechnology company focused on developing and commercializing genetic medicines for patients with rare diseases. Using our patented platform that is based on engineered HSV-1, we create vectors that efficiently deliver therapeutic transgenes to cells of interest in multiple organ systems. The cell's own machinery then transcribes and translates the encoded effector to treat or prevent disease. We formulate our vectors for non-invasive or minimally invasive routes of administration at a healthcare professional's office or potentially in the patient's home by a healthcare professional. Our goal is to develop easy-to-use medicines to dramatically improve the lives of patients living with rare diseases and chronic conditions. Our innovative technology platform is supported by in-house, commercial scale Current Good Manufacturing Practice ("CGMP") manufacturing capabilities.

Liquidity

As of December 31, 2022, the Company had an accumulated deficit of $280.8 million. As the Company continues to incur losses, a transition to profitability is dependent upon the successful development, approval and commercialization of its product candidates and the achievement of a level of revenues adequate to support the Company's cost structure. The Company may never achieve profitability, and unless and until it does the Company will continue to need to raise additional capital or obtain financing from other sources. Management intends to fund future operations through its on hand cash and cash equivalents, the sale of equity, and debt financings and may also seek additional capital through arrangements with strategic partners or other sources. There can be no assurance that additional funding will be available on terms acceptable to the Company, if at all.

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to the failure of product candidates in clinical and preclinical studies, the development of competing product candidates or other technological innovations by competitors, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to commercialize product candidates. The Company expects to incur significant costs to expand it's commercialization capabilities in advance of the potential global regulatory approvals of it's lead product, B-VEC. The Company believes that its cash, cash equivalents and short-term investments of approximately $379.2 million as of December 31, 2022 will be sufficient to allow the Company to fund its planned operations for at least the next 12 months from the date of this Annual Report on Form 10-K.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the United States of America ("GAAP"). All intercompany balances and transactions have been eliminated in consolidation. Certain prior period amounts have been reclassified to conform to the current period presentation. The reclassified amounts have no impact on the Company's previously reported financial position or results of operations.

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the consolidated financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including: expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be

representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. Estimates are used in the following areas, including: stock-based compensation expense, accrued expenses, the fair value of financial instruments, the incremental borrowing rate for lease liabilities, and the valuation allowance included in the deferred income tax calculation.

Segment and Geographical Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company and the Company's chief operating decision maker view the Company's operations and manage its business in one operating segment, which is the business of developing and commercializing pharmaceutical products.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to credit risk consist of cash, cash equivalents and investments. The Company's policy is to invest its cash, cash equivalents and investments in money market funds, corporate bonds, commercial paper, government agency securities and various other bank deposit accounts. The counterparties to the agreements relating to the Company's investments consist of financial institutions of high credit standing. The Company is exposed to credit risk in the event of default by the financial institutions to the extent amounts recorded on the consolidated balance sheets are in excess of insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no financial instruments with off-balance sheet risk of loss.

Cash, Cash Equivalents and Investments

Cash and cash equivalents consist of money market funds and bank deposits. Cash equivalents are defined as short-term, highly liquid investments with original maturities of 90 days or less at the date of purchase.

Investments with maturities of less than one year are classified as short-term investments on the consolidated balance sheets and consist of commercial paper, corporate bonds, and government agency securities. Investments with maturities of greater than one year are classified as long-term investments on the consolidated balance sheets and consist of corporate bonds and government agency securities. Accrued interest on investments is also classified as short-term investments.

As our entire investment portfolio is considered available for use in current operations, we classify all investments as available-for-sale securities. Available-for-sale securities are carried at fair value, with unrealized gains and losses reported in accumulated other comprehensive loss, which is a separate component of stockholders' equity in the consolidated balance sheets. Any premium arising at purchase is amortized to the earliest call date and any discount arising at purchase is accreted to maturity. Amortization and accretion of premiums and discounts are recorded in interest and other income, net, or general and administrative expenses in the consolidated statements of operations.

Fair Value of Financial Instruments

Fair value is defined as the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. There is a three-level hierarchy that prioritizes the inputs used in determining fair value by their reliability and preferred use, as follows:

- *Level 1*—Valuations based on quoted prices in active markets for identical assets or liabilities.
- *Level 2*—Valuations based on quoted prices in active markets for similar assets and liabilities, quoted prices for identical or similar assets and liabilities in inactive markets, or other inputs that are observable, or can be corroborated by observable market data.
- *Level 3*—Valuations based on inputs that are both significant to the fair value measurement and unobservable.

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

There have been no significant changes to the valuation methods utilized by the Company during the periods presented. There have been no transfers between Level 1, Level 2, and Level 3 in any periods presented.

The carrying amounts of financial instruments consisting of cash and cash equivalents, investments, prepaid expenses and other current assets, accounts payable, accrued expenses and other current liabilities included in the Company's consolidated financial statements, are reasonable estimates of fair value, primarily due to their short maturities.

Our available-for-sale, short-term and long-term investments, which consist of commercial paper, corporate bonds, and U.S. government agency securities are considered to be Level 2 financial instruments. The fair value of Level 2 financial assets is determined using inputs that are observable in the market or can be derived principally from or corroborated by observable market data such as pricing for similar securities, recently executed transactions, cash flow models with yield curves, and benchmark securities. In addition, Level 2 financial instruments are valued using comparisons to like-kind financial instruments and models that use readily observable market data as their basis.

Property and Equipment, net

Property and equipment, net, is stated at cost, less accumulated depreciation. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred, while costs of major additions and betterments are capitalized. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, which are as follows:

Computer equipment and software	3 - 7 years
Laboratory and manufacturing equipment	3 - 20 years
Furniture and fixtures	3 - 7 years
Leasehold improvements	lesser of remaining useful life or remaining life of lease

The Company reviews the estimated useful lives of its property and equipment on a continuing basis. In evaluating the useful lives, the Company considers how long assets will remain functionally effective, whether the technology continues to be relevant and considers other competitive and economic factors. If the assessment indicates that the assets will be used for a shorter or longer period than previously anticipated, the useful life of the assets is adjusted, resulting in a change in estimate. Changes in estimates are accounted for on a prospective basis by depreciating the current carrying values of the assets over their revised remaining useful lives.

A review performed by the Company in the current year indicated that certain pieces of lab equipment would be functional for a longer term than previously estimated and as a result, the Company increased the useful lives of these assets from 7 to 15 years. This change was effective and accounted for prospectively beginning in Q3 2022. The effect of this change in useful life estimate did not result in a material change to depreciation expense for the year ended December 31, 2022.

Construction-in-progress ("CIP") is not depreciated until the asset is placed in service.

Impairment of Long-Lived Assets

The Company evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. We review the recoverability of the net book value of long-lived assets whenever events and circumstances indicate ("triggering events") that the net book value of an asset may not be recoverable from the estimated undiscounted future cash flows expected to result from its use and eventual disposition. In cases where a triggering event occurs and undiscounted expected future cash flows are less than the net book value, we recognize an impairment loss equal to an amount by which the net book value exceeds the fair value of the asset. Long-lived assets to be disposed of are reported at the lower of carrying amount or fair value less cost to sell. The Company not experienced any triggering events or recognized any impairment losses for the years ended December 31, 2022, 2021, and 2020.

Leases

The Company accounts for its lease agreements in accordance with FASB ASC Topic 842, *Leases*. Right-of-use lease assets represent the right to use an underlying asset during the lease term and the lease liabilities represent the commitment to make lease payments arising from the lease. Right-of-use lease assets and obligations are recognized based on the present value of remaining lease payments over the lease term. As the Company's existing lease agreements do not provide an implicit rate and as the Company does not have any external borrowings, the Company has used an estimated incremental borrowing rate based on the information available at lease commencement in determining the present value of lease payments. Operating lease expense is recognized on a straight-line basis over the lease term. Variable lease expense is recognized in the period in which the obligation for the payment is incurred. In addition, the Company also has made an accounting policy election to exclude leases with an initial term of twelve months or less from its consolidated balance sheets and to account for lease and non-lease components of its operating leases as a single component.

For lease arrangements where it has been determined that the Company has control over an asset that is under construction and is thus considered the accounting owner of the asset during the construction period, the Company records a construction in progress asset and corresponding financial obligation on the consolidated balance sheet. Once the construction is complete, an assessment is performed to determine whether the lease meets certain "sale-leaseback" criteria. If the sale-leaseback criteria are determined to be met, the Company will remove the asset and related financial obligation from the consolidated balance sheet and treat the lease as either an operating or finance lease based on an assessment of the guidance. If, upon completion of construction, the project does not meet the "sale-leaseback" criteria, the lease will be treated as a financing obligation and the Company will depreciate the asset over its estimated useful life for financial reporting purposes once the asset has been placed into service.

Research and Development Expenses

Research and development costs are charged to expense as incurred in performing research and development activities. These costs include employee compensation costs, facilities and overhead, preclinical and clinical activities, clinical manufacturing costs, contract management services, regulatory and other related costs.

The Company estimates contract research and manufacturing expenses based on the services performed pursuant to contracts with research organization and manufacturing organizations that manufacture materials used in the Company's ongoing preclinical and clinical studies. Non-refundable advanced payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. These estimates are based on communications with third-party service providers and the Company's estimates of accrued expenses using information available at each balance sheet date. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual accordingly.

Stock-Based Compensation Expense

The Company applies the fair value recognition provisions of Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") Topic 718, *Compensation—Stock Compensation* ("ASC 718"), to account for stock-based compensation. Compensation costs related to stock options granted are based on the estimated fair value of the awards on the date of grant.

ASC 718 requires all stock-based payments, including grants of stock options and restricted stock, to be recognized in the consolidated statements of operations based on their grant-date fair values. Compensation expense is recognized on a straight-line basis based on the grant-date fair value over the associated service period of the award, which is generally the vesting term.

The Company estimates the fair value of its stock options using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including: (i) the expected stock price volatility; (ii) the expected term of the award; (iii) the risk-free interest rate; and (iv) expected dividends. Once the Company's own sufficient historical volatility data was obtained in 2021, the Company eliminated the use of a representative peer group and began using only its own historical volatility data in its estimate of expected volatility.

The Company estimates the expected term of its stock options using the "simplified" method, whereby the expected term equals the arithmetic mean of the vesting term and the original contractual term of the option. The risk-free interest rates are based on US Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid and does not expect to pay dividends in the foreseeable future. The Company accounts for forfeitures as they occur. Stock-based compensation expense recognized in the financial statements is based on awards for which service conditions are expected to be satisfied.

Income Taxes

For the years ended December 31, 2022, 2021, and 2020, income taxes were recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Under this method, we record deferred tax assets and liabilities for the expected future tax consequences of temporary differences between the financial statement carrying amounts and the tax basis of assets and liabilities using enacted tax rates expected to be in effect when the differences are expected to reverse. Valuation allowances are provided when necessary to reduce net deferred tax assets to the amount that is more likely than not to be realized. Based on the available evidence, we are unable, at this time, to support the determination that it is more likely than not that our deferred tax assets will be utilized in the future. Accordingly, we recorded a full valuation allowance as of December 31, 2022 and 2021. We intend to maintain a valuation allowance until sufficient evidence exists to support its reversal.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2022 and 2021, the Company did not have any significant uncertain tax positions.

The Company may recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022 and 2021, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss.

Comprehensive Loss

Comprehensive loss is defined as the change in equity during a period from transactions from non-owner sources. Unrealized gains or losses on available-for-sale securities is a component of other comprehensive gains or losses and is presented net of taxes. We record reclassifications from other comprehensive gains or losses to interest and other income, net on the consolidated statements of operations related to realized gains on sales of available-for-sale securities.

The Company reviews its securities quarterly to determine whether an other-than-temporary impairment has occurred. The Company determined that there were no other-than-temporary impairments during the years ended December 31, 2022, 2021, and 2020.

Recent Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB that the Company adopts as of the specified effective date. There were no recently adopted accounting pronouncements that had a material impact on the Company's financial statements, and no recently issued accounting pronouncements that are expected to have a material impact on the Company's financial statements.

3. Net Loss Per Share Attributable to Common Stockholders

Basic net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share attributable to common stockholders is computed by dividing the net loss by the weighted-average number of shares of common stock and common share equivalents outstanding for the period. Common share equivalents consist of common stock issuable upon exercise of stock options and vesting of restricted stock awards. There were 3,582,181, 2,043,179, and 853,614 common share equivalents outstanding in the form of stock options and 66,600, 98,800, and zero unvested restricted stock awards as of December 31, 2022, 2021 and 2020, respectively, that have been excluded from the calculation of diluted net loss per common share as their effect would be anti-dilutive for all periods presented.

(In thousands, except share and per share data)	**Years Ended December 31,**		
	2022	**2021**	**2020**
Net loss per common share	$ (139,975)	$ (69,570)	$ (32,167)
Weighted-average basic and diluted common shares	25,491,721	22,196,846	18,787,161
Basic and diluted net loss per common share	$ (5.49)	$ (3.13)	$ (1.71)

4. Fair Value Instruments

The following tables show the Company's cash, cash equivalents and available-for-sale securities by significant investment category as of December 31, 2022 and 2021, respectively (in thousands):

	December 31, 2022						
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Aggregate Fair Value	Cash and Cash Equivalents	Short-term Marketable Securities (1)	Long-term Marketable Securities (2)
Level 1:							
Cash and cash equivalents	$ 161,900	$ —	$ —	$ 161,900	$ 161,900	$ —	$ —
Subtotal	161,900	—	—	161,900	161,900	—	—
Level 2:							
Commercial paper	63,624	5	(23)	63,606	—	63,606	—
Corporate bonds	82,241	13	(419)	81,835	—	77,214	4,621
U.S government agency securities	76,683	161	(393)	76,451	—	76,451	—
Subtotal	222,548	179	(835)	221,892	—	217,271	4,621
Total	$ 384,448	$ 179	$ (835)	$ 383,792	$ 161,900	$ 217,271	$ 4,621

	December 31, 2021						
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Aggregate Fair Value	Cash and Cash Equivalents	Short-term Marketable Securities (1)	Long-term Marketable Securities (2)
Level 1:							
Cash and cash equivalents	$ 341,246	$ —	$ —	$ 341,246	$ 341,246	$ —	$ —
Subtotal	341,246	—	—	341,246	341,246	—	—
Level 2:							
Commercial paper	40,469	1	(4)	40,466	—	40,466	—
Corporate bonds	83,300	10	(114)	83,196	—	35,768	47,428
U.S government agency securities	37,621	—	(62)	37,559	—	20,616	16,943
Subtotal	161,390	11	(180)	161,221	—	96,850	64,371
Total	$ 502,636	$ 11	$ (180)	$ 502,467	$ 341,246	$ 96,850	$ 64,371

(1) The Company's short-term marketable securities mature in one year or less.
(2) The Company's long-term marketable securities mature between one year and two years.

See Note 2 to these consolidated financial statements for additional discussion regarding the Company's fair value measurements.

5. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consist of the following as of December 31, 2022 and 2021, respectively (in thousands):

	December 31, 2022	December 31, 2021
Construction-in-progress	$ 131,331	$ 104,340
Leasehold improvements	24,217	5,723
Furniture and fixtures	957	891
Computer equipment and software	100	85
Laboratory and manufacturing equipment	11,872	5,530
Total property and equipment	168,477	116,569
Accumulated depreciation and amortization	(6,793)	(4,214)
Property and equipment, net	$ 161,684	$ 112,355

Depreciation expense was $2.6 million, $1.8 million and $1.5 million for the years ended December 31, 2022, 2021, and 2020, respectively.

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following as of December 31, 2022 and 2021, respectively (in thousands):

	December 31, 2022	December 31, 2021
Accrued preclinical and clinical expenses	$ 1,365	$ 1,602
Accrued professional fees	3,397	2,011
Accrued payroll and benefits	6,781	2,882
Accrued construction in progress	11,452	9,606
Accrued financing fees	—	26
Accrued taxes	43	83
Other current liabilities	267	87
Total	$ 23,305	$ 16,297

6. Commitments and Contingencies

Significant Contracts and Agreements

Agreements with Contract Manufacturing Organizations and Contract Research Organizations

The Company enters into various agreements in the normal course of business with Contract Research Organizations ("CROs"), Contract Manufacturing Organizations ("CMOs") and other third parties for preclinical research studies, clinical trials and testing and manufacturing services. The agreements with CMOs relate to the manufacturing of sterile gel that is mixed with in-house produced vectors as part of the final drug product applied in certain of our clinical trials. These agreements may also include research and development activities, storage, packaging, labeling, and/or testing of our preclinical and clinical-stage products. The Company is obligated to make milestone payments under certain of these agreements. The estimated remaining commitment as of December 31, 2022 under these agreements is approximately $2.1 million. The Company may also be responsible for the payment of a monthly service fee for project management services for the duration of any agreements. The Company has incurred research and development expenses under these agreements of $6.0 million, $5.0 million and $4.6 million for the years ended December 31, 2022, 2021, and 2020, respectively.

Commercial Preparedness Activities

The Company has contracted with various third parties to facilitate, coordinate and perform agreed upon commercial preparedness and market research activities relating to our lead product candidate, B-VEC. These contracts typically call for the payment of fees for services upon the achievement of certain milestones or as services are rendered. The estimated remaining commitment as of December 31, 2022 is $8.4 million. The Company has incurred expenses under these activities of $14.2 million, $6.1 million and $1.9 million for the years ended December 31, 2022, 2021, and 2020, respectively.

ASTRA Contractual Obligations

The Company has contracted with various third parties to complete the interior build-out of our second CGMP facility, ASTRA. Additionally, the Company has entered into various non-cancellable purchase agreements for long-lead materials to help avoid potential schedule disruptions or material shortages. These contracts typically call for the payment of fees for services or materials upon the achievement of certain milestones. The estimated remaining commitment as of December 31, 2022 is $16.3 million. The Company has included costs incurred to-date associated with ASTRA within construction-in-progress as of December 31, 2022.

In June 2021, the Company entered into a Standard Form of Contract for Construction and the corresponding General Conditions of the Contract for Construction (collectively, the "Agreement") with The Whiting-Turner Contracting Company ("Whiting-Turner"), pursuant to which Whiting-Turner is constructing and managing the construction of ASTRA. Subject to certain conditions in the Agreement, the Company will pay Whiting-Turner a contract price consisting of the cost of work plus a fee equal to 1.75% of the cost of work.

Effective September 2021, the Company entered into a guaranteed maximum price amendment (the "Amendment") to the Agreement to set forth the guaranteed maximum price, as well as the date by which Whiting-Turner is to achieve Substantial Completion (as defined in the Agreement). Under the Amendment, the guaranteed maximum price to be paid by the Company, which has been amended from time to time for change orders additional work is awarded to Whiting-Turner, is currently $85.5 million. Whiting-Turner's work under the Agreement represents a portion of the work necessary to complete construction of the ASTRA facility and, therefore the date of Substantial Completion of Whiting-Turner's work under the Agreement may not equate to the date of completion of ASTRA. The guaranteed maximum price under the Agreement with Whiting-Turner constitutes only a portion of the total estimated cost of building and equipping ASTRA as there are various other third parties engaged in the project for which contracts are not individually material.

Legal Proceedings

In May 2020, a complaint was filed against the Company in the United States District Court for the Western District of Pennsylvania by PeriphaGen, Inc. ("PeriphaGen"), which also named our Chief Executive Officer and President, R&D, Krish Krishnan and Suma Krishnan, respectively. The complaint alleged breach of contract and misappropriation of trade secrets, which secrets the plaintiff asserts were used to develop our product candidates, including the vector backbones, and our STAR-D platform. We answered the complaint in June 2020 by denying the allegations and brought a counterclaim asking the court to declare that we did not misappropriate PeriphaGen's trade secrets or confidential information, and to further declare that we are the rightful and sole owner of our product candidates and STAR-D platform. In addition, the Company filed a third-party complaint against two principals of PeriphaGen, James Wechuck and David Krisky, alleging breach of contract and seeking contribution and indemnification from them in the event PeriphaGen is awarded damages.

On March 9, 2022, the court officially ordered the parties to attend mediation on March 11, 2022. During the course of the mediation process, the parties were able to exchange information, allowing the parties to value their positions. On March

12, 2022, the Company entered into a binding term sheet to settle the dispute. In April 2022, the Company entered into a final settlement agreement and paid PeriphaGen an upfront payment of $25.0 million on April 28, 2022 for: (i) the release of all claims in the trade secret litigation with PeriphaGen; (ii) the acquisition of certain PeriphaGen assets, and (iii) the grant of a license by PeriphaGen for dermatological applications. Upon approval of the Company's first product by the U.S. Food and Drug Administration, the Company will pay PeriphaGen an additional $12.5 million, followed by three additional $12.5 million contingent milestone payments upon reaching $100.0 million in total cumulative sales, $200.0 million in total cumulative sales and $300.0 million in total cumulative sales. As defined in the settlement agreement, cumulative sales shall include all revenue from sales of the Company products by the Company and its affiliates and licensees, as reported by the Company in its annual Form 10-K filings. If all milestones are achieved, the total consideration for settling the dispute, acquiring certain assets, and granting of a license from PeriphaGen will be $75.0 million.

The Company recorded the $25.0 million within litigation settlement expense on the consolidated statements of operations for the year ended December 31, 2022. The additional contingent milestone payments were not deemed probable due to uncertainty in the achievement of these milestones as of December 31, 2022, and therefore no additional accrual has been recorded.

The Company has received $1.1 million and $1.6 million of insurance proceeds during fiscal years ending December 31, 2022 and 2021, respectively. Additionally, the Company had outstanding receivables of zero and $560 thousand as of December 31, 2022 and 2021, respectively, recorded within prepaid expenses and other current assets on the consolidated balance sheets, as management determined that the amounts were probable of collection. The reimbursements have been recorded as an offset to our legal fees included in general and administrative expenses on the consolidated statements of operations and within operating activities on the consolidated statements of cash flows.

7. Leases

Lease Agreements

In May 2016, the Company signed an operating lease for laboratory and office space in Pittsburgh, Pennsylvania that commenced in June 2016 and was scheduled to expire in October 2017 (the “2016 Lease”). The 2016 Lease has been amended several times to increase the area leased, which currently consists of approximately 54,000 square feet and includes the commercial scale CGMP-compliant manufacturing facility, (“ANCORIS”). As a result of the lease amendments, the 2016 Lease expiration date was extended to October 2031. In September 2022, the Company amended the 2016 Lease (“Short-Term Amendment”) to add a short-term lease for additional office space that commenced in October 2022 and expires on September 2023. The Short-Term Amendment increased the area leased by approximately 7,000 square feet through September 2023. Due to the short-term nature of this amendment and the Company's lease accounting policy, the Company did not record a right-of-use asset or corresponding lease liability.

In December 2019, the Company entered into a lease agreement for a second commercial gene therapy facility, (“ASTRA”), in the Pittsburgh, Pennsylvania area (“ASTRA lease”) with Northfield I, LLC (the “Landlord”, “Northfield”, or “Lessor”) with an initial lease term that expired on October 2035. The ASTRA lease contained an option (“Purchase Option”) to purchase the building, related improvements and take corresponding assignment of the Landlord's rights under its existing Ground Lease (the “Ground Lease”).

In October 2020, the Company was provided with notice that the initial delivery conditions of the building had been met, including completion of the building shell, interior slab, and exterior doors, and the Company gave the Landlord notice of its intent to purchase ASTRA for approximately $9.4 million, subject to the parties entering into a commercially reasonable purchase and sale agreement. As a result of the Company's ability to exercise its option to purchase ASTRA, the Company obtained control over the construction in progress of ASTRA. The Company recorded a $10 million CIP asset and a corresponding build-to-suit lease liability related to the costs incurred by the Landlord, offset by the previous cash contributions of $2.4 million.

In January 2021, the Company entered into a Purchase and Sale Agreement ("PSA") for ASTRA with Northfield related to the purchase option exercised by the Company in October 2020, for a purchase price of $9.4 million. The Company held approximately $1.5 million on deposit with Northfield under the existing lease agreement and applied this deposit as a credit against the purchase price at closing. In February 2021, Northfield delivered the space as substantially complete and made the space available for access by the Company, thus triggering lease commencement. As a result, the Company concluded that this transaction did not qualify for sale-leaseback accounting because it did not meet the definition of a sale. As control did not transfer to the Lessor at lease commencement, the transaction continued to be accounted for as construction in progress and a financing obligation. In March 2021, the purchase closed and the Company determined that reclassification of the construction in progress to buildings and leasehold improvements was not appropriate as the interior of the building was not yet ready for its intended use. From construction completion to the closing of the purchase, the Company recognized interest expense to accrete the financial obligation to a balance that equaled the cash consideration that was paid upon the close of purchase. The building continues to be held under construction-in-progress as of December 31, 2022. The interior of the building is currently under construction and is expected to be completed and validated in 2023. For more information about the expected construction costs associated with ASTRA, see "ASTRA Contractual Obligations" below.

As part of the transaction, the Company also became the accounting owner of the Ground Lease, due to obtaining control over ASTRA, and recorded the applicable operating right-of-use asset and corresponding lease liability in October 2020. When the PSA was finalized, the Company took assignment of the Lessor's Ground Lease, in accordance with the Purchase Option, of which lease payments are based on annual payments of $82 thousand, and are subject to a cumulative 10% escalation clause every 5 years through 2071.

In December 2021, the Company entered into a 3 year lease agreement for the Boston, Massachusetts office that commenced in January 2022 and expires in January 2025.

In May 2022, the Company entered into a 16 month lease agreement for the Zug, Switzerland office that commenced in September 2022 and expires December 2023.

As of December 31, 2022, future minimum commitments under the Company's operating leases were as follows (in thousands):

	Operating Leases
2023	$ 1,648
2024	1,539
2025	1,277
2026	1,277
2027	1,300
Thereafter	10,762
Future minimum operating lease payments	$ 17,803
Less: Interest	8,870
Present value of lease liability	$ 8,933

Supplemental balance sheet information related to leases is as follows:

	December 31, 2022	December 31, 2021
Operating leases:		
Right-of-use assets	$ 8,042	$ 7,228
Current portion of lease liability	1,561	1,041
Lease liability	7,372	6,983
Total lease liability	$ 8,933	$ 8,024
Weighted average remaining lease term, in years	12.5	14.4
Weighted average discount rate	9.4 %	9.5 %

The components of the Company's lease expense are as follows:

	Years Ended December 31,		
	2022	**2021**	**2020**
Lease cost:			
Operating lease expense	$ 1,532	$ 1,275	$ 767
Variable lease expense	226	160	57
Total lease expense	$ 1,758	$ 1,435	$ 824

8. Capitalization

Sale of Common Stock

In December 2021, the Company completed an underwritten public offering of 2,866,667 shares of its common stock, including 200,000 shares purchased by the underwriters pursuant to their option to purchase additional shares, at $75.00 per share. Net proceeds to the Company from the offering were $201.9 million after deducting underwriting discounts and commissions of approximately $12.9 million, and other offering expenses payable by the Company of $227 thousand.

In February 2021, the Company completed an underwritten public offering of 2,211,538 shares of its common stock, including 288,461 shares purchased by the underwriters pursuant to their option to purchase additional shares, at $65.00 per share. Net proceeds to the Company from the offering were $134.9 million after deducting underwriting discounts and commissions of approximately $8.6 million, and other offering expenses payable by the Company of $198 thousand.

In May 2020, the Company completed a public offering of 2,275,000 shares of its common stock to the public at $55.00 per share. Net proceeds to the Company from the offering were $117.2 million after deducting underwriting discounts and commissions of approximately $7.5 million, and other offering expenses payable by the Company of approximately $463 thousand.

ATM Program

The Company sells shares of common stock from time to time pursuant to its previously executed sales agreement (the "Sales Agreement") with Cowen and Company, LLC (“Cowen”) with respect to an at-the-market equity offering program (“ATM”) finalized on December 31, 2020, under which Cowen acts as the Company's agent and/or principal and may issue and sell from time to time, during the term of the Sales Agreement, shares of common stock having an aggregate offering price up to $150.0 million (“Placement Shares”). The issuance and sale of the Placement Shares by the Company under the Sales Agreement are made pursuant to the Company's effective “shelf” registration statement on Form S-3. During 2021, the Company issued and sold 262,500 shares of common stock at a weighted average price of $66.50 per share for net proceeds of $16.9 million after deducting selling commissions of approximately $524 thousand. During the year ended December 31, 2022, the Company issued and sold 434,782 shares of common stock at a weighted average price of $69.00 per share for net proceeds of $29.1 million after deducting selling commissions of approximately $900 thousand, resulting in a remaining $102.5 million available for issuance under the ATM Program.

9. Stock-Based Compensation

Stock Options

In 2017, the Company adopted the 2017 IPO Stock Plan (the “Plan”), which governs the issuance of stock options to employees, certain non-employee consultants, and directors. Initially, the Company reserved 900 thousand shares for issuance under the Plan with an initial sublimit for incentive stock options of 900 thousand shares. On an annual basis, the amount of shares available for issuance under the Plan increases by an amount equal to four percent of the total outstanding shares as of the last day of the preceding calendar year. The sublimit of incentive stock options is not subject to the increase.

Options granted to employees and non-employees vest ratably over a four-year period and stock options granted to directors of the company vest ratably over one-year to three-year periods. Stock options have a life of ten years.

The Company granted 2,130,500 and 1,422,450 stock options to employees, non-employees, and directors during the years ended December 31, 2022 and 2021, respectively.

The following table summarizes the Company's stock option activity:

	Stock Options Outstanding	Weighted-average Exercise Price	Weighted-average Remaining Contractual Life (Years)	Aggregate Intrinsic Value (In thousands) (1)
Balance at January 1, 2021	853,614	$ 40.31	9.0	$ 16,804
Granted	1,422,450	66.88		
Exercised	(54,260)	38.12		
Cancelled or forfeited	(175,750)	61.35		
Expired	(2,875)	75.82		
Balance at December 31, 2021	2,043,179	$ 57.00	9.0	$ 31,331
Granted	2,130,500	64.14		
Exercised	(138,855)	50.47		
Cancelled or forfeited	(438,892)	59.22		
Expired	(13,751)	78.80		
Balance at December 31, 2022	3,582,181	$ 61.50	8.7	$ 64,880
Exercisable at December 31, 2022	666,886	$ 49.20	7.5	$ 20,055

(1) Aggregate intrinsic value represents the difference between the closing stock price of our common stock on December 31, 2022 and the exercise price of outstanding in-the-money options.

The total intrinsic value (the amount by which the fair market value exceeded the exercise price) of stock options exercised during the years ended December 31, 2022 and 2021 was $2.9 million and $1.3 million, respectively.

The weighted-average grant-date fair value per share of options granted to employees, non-employees, and directors during the years ended December 31, 2022 and 2021 was $44.50 and $43.05, respectively.

There was $104.4 million of unrecognized stock-based compensation expense related to employees', non-employees', and directors' awards that is expected to be recognized over a weighted-average period of 2.9 years as of December 31, 2022.

The Company has recorded aggregate stock-based compensation expense related to the issuance of stock option awards in the consolidated statements of operations for the years ended December 31, 2022, 2021, and 2020 as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Research and development	$ 7,897	$ 3,434	$ 994
General and administrative	23,551	10,235	2,278
Total stock-based compensation	$ 31,448	$ 13,669	$ 3,272

We capitalize the portion of stock-based compensation that relates to work performed on the construction of manufacturing facilities. There was $551 thousand, $284 thousand, and $34 thousand of stock-based compensation that was capitalized in the years ended December 31, 2022, 2021, 2020, respectively.

The fair value of options granted was estimated at the date of grant using the Black-Scholes valuation model with the following weighted-average assumptions for the years ended December 31, 2022, 2021, and 2020:

	Years Ended December 31,		
	2022	2021	2020
Expected stock price volatility	78 %	72 %	75 %
Expected term of the award (years)	6.2	6.2	6.2
Risk-free interest rate	2.42 %	1.10 %	0.64 %
Weighted average exercise price	$ 64.14	$ 66.88	$ 47.29
Forfeiture Rate	— %	— %	14.74 %
Dividend Yield	— %	— %	— %

Restricted Stock Awards

Restricted stock awards ("RSAs") granted to employees vest ratably over a four-year period. The Company granted zero and 98,800 RSAs to employees of the Company during the year ended December 31, 2022 and 2021 respectively.

The following table summarizes the Company's RSA activity:

	Number of Shares	Weighted Average Grant Date Fair Value
Non-vested RSAs as of December 31, 2021	98,800	$ 78.89
Granted	—	—
Vested	(14,321)	78.89
Surrendered or forfeited	(17,879)	78.89
Non-vested RSAs as of December 31, 2022	66,600	$ 78.89

There was $3.8 million of unrecognized stock-based compensation expense related to employees' awards that is expected to be recognized over a weighted-average period of 2.2 years as of December 31, 2022.

The Company recorded the following stock-based compensation expense related to RSAs within general and administrative expenses in the accompanying consolidated statements of operations (in thousands):

	Years Ended December 31,		
	2022	2021	2020
General and administrative	$ 1,782	$ 1,650	$ —
Total stock-based compensation	$ 1,782	$ 1,650	$ —

Shares remaining available for grant under the Company's stock incentive plan were 469,616, with a remaining sublimit for incentive stock options of 5,581, at December 31, 2022.

10. Income Taxes

The Company did not record a current or deferred income tax expense or benefit for the years ended December 31, 2022 and 2021 due to the valuation allowance position. A reconciliation of income tax (benefit) expense computed at the statutory federal and state income tax rate for the year to income tax (benefit) expense as reflected in our financial statements for years ended December 31, 2022, 2021 and 2020 are as follows (in thousands):

	Years Ended December 31,		
	2022	2021	2020
Federal income tax (benefit) at statutory rate	$ (29,395)	$ (14,578)	$ (6,752)
Change in valuation allowance	39,781	20,689	11,112
State income tax expense net of federal benefit	(10,438)	(5,436)	(2,632)
Credits	(1,736)	(1,295)	(887)
Other non-deductible expenses	2,182	675	(216)
Other	(394)	(55)	(625)
Total tax expense (benefit)	$ —	$ —	$ —

The significant components of the Company's deferred tax assets and liabilities as of December 31, 2022 and 2021 are as follows (in thousands):

	December 31, 2022	December 31, 2021
Deferred tax assets:		
Net operating loss carryforwards	$ 52,569	$ 33,170
Stock compensation	7,445	3,906
Lease liability	2,572	2,344
Depreciation	—	679
Accrued expenses	2,206	817
Capitalized costs	14,124	884
Credits	6,708	3,607
Unrealized loss on marketable securities	192	49
Total deferred tax assets	85,816	45,456
Valuation allowance	(82,513)	(42,732)
Deferred tax assets	$ 3,303	$ 2,724
Deferred tax liabilities:		
Depreciation	(137)	—
Right-of-use assets	(2,312)	(2,111)
Prepaid expenses	(854)	(613)
Total deferred tax liabilities	$ (3,303)	$ (2,724)
Net deferred tax assets	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of operating losses, the Company has concluded that it is not more likely than not that the benefit of its deferred tax assets will be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2022 and 2021.

As of December 31, 2022 and 2021, the Company had federal research and development credit carryforwards of approximately $2.0 million and $2.4 million, respectively. The federal tax credit carryforwards will begin to expire in 2039 if not utilized. As of December 31, 2022 and 2021, the Company also had orphan drug tax credit carryforwards of approximately $4.4 million and $910 thousand, respectively. The orphan drug tax credit carryforwards will begin to expire in 2038 if not utilized.

As of December 31, 2022 and 2021, the Company had state research and development credit carryforwards of approximately $457 thousand and $321 thousand, respectively. The state tax credit carryforwards will begin to expire in 2032 if not utilized.

As of December 31, 2022, the Company had cumulative U.S. federal NOL carryforwards of approximately $177.7 million. Of this amount, $5.0 million is available to offset future income tax liabilities and will expire in 2037, the remaining $172.7 million is available indefinitely to offset future income tax liabilities with no expiration period.

As of December 31, 2022, the Company had cumulative U.S. state NOL carryforwards of approximately $186.0 million. The state NOLs are available to offset future state income tax liabilities and will begin to expire in 2037.

Under the provisions of the Internal Revenue Code, the NOL carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Internal Revenue Code Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities.

No deferred tax assets have been recognized on our consolidated balance sheets related to these NOLs, as they are fully offset by a valuation allowance. If we have previously had, or have in the future, one or more Section 382 "ownership changes," including in connection with our initial public offering or another offering, or if we do not generate sufficient taxable income, we may not be able to utilize a material portion of our NOLs, even if we achieve profitability.

The Company files income tax returns in the United States at the federal and state level and in foreign jurisdictions in which the Company conducts business activities. The federal and state income tax returns are subject to tax examinations for the tax year ended December 31, 2019, 2020 and 2021. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period. Additionally, the Company is subject to tax examinations by taxing authorities in foreign jurisdictions where it has business operations. At this time, the Company is not undergoing examination by the Internal Revenue Service or any foreign taxing authorities.

11. Subsequent Events

The Company evaluates events or transactions that occur after the balance sheet date, but prior to the issuance of the financial statements, to identify matters that require disclosure. The Company concluded that no subsequent events have occurred that would require recognition or disclosure in the consolidated financial statements.

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

As previously reported in the Company's Current Report on Form 8-K filed on May 26, 2022, effective May 24, 2022, the Audit Committee of the Company's Board of Directors dismissed Mayer Hoffman McCann P.C. as the Company's independent registered public accounting firm effective immediately and approved the engagement of KPMG LLP as the Company's new independent registered public accounting firm, commencing for its quarter ending June 30, 2022 and the Company's fiscal year ending December 31, 2022. For more information, please refer to the Company's Current Report on Form 8-K filed on May 26, 2022.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Under the supervision of our Chief Executive Officer and Chief Accounting Officer, we evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act) as of December 31, 2022. Based on that evaluation, our Chief Executive Officer and Chief Accounting Officer have concluded that our disclosure controls and procedures were effective as of December 31, 2022 to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Accounting Officer, as appropriate to allow timely discussion regarding required disclosures. In designing and evaluating our disclosure controls and procedures, management recognizes that any disclosure controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply its judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Exchange Act Rules 13a-15(f) and 15d-15(f). Our management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2022 based on the criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

Based on the results of its evaluation, management concluded that our internal control over financial reporting was effective as of December 31, 2022. The effectiveness of our internal control over financial reporting as of December 31, 2022 has been audited by KPMG, an independent registered public accounting firm, as stated in their report which is included herein.

Inherent Limitations on Controls and Procedures

Our management, including the Chief Executive Officer and Chief Accounting Officer, do not expect that our disclosure controls and procedures and our internal controls will prevent all error and all fraud. A control system, no matter how well designed and operated, can only provide reasonable assurances that the objectives of the control system are met. The design of a control system reflects resource constraints; the benefits of controls must be considered relative to their costs. Because there are inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been or will be detected. As these inherent limitations are known features of the financial reporting process, it is possible to design into the process safeguards to reduce, though not eliminate, these risks. These inherent limitations include the realities that judgments in decision-making can be faulty and that breakdowns occur because of simple error or mistake. Controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls is based in part upon certain assumptions about the likelihood of future events. While our disclosure controls and procedures are designed to provide reasonable assurance of achieving their objectives, there can be no assurance that any design will succeed in achieving its stated goals under all future conditions. Over time, controls may become inadequate because of changes in conditions or deterioration in the degree of compliance with the policies or procedures. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We intend to review and evaluate the design and effectiveness of our disclosure controls and procedures on an ongoing basis and to improve our controls and procedures over time and to correct any deficiencies that we may discover in the future. While our Chief Executive Officer and Chief Accounting Officer have concluded that, as of December 31, 2022, the design of our disclosure controls and procedures, as defined in Rule 13a-15(e) under the Exchange Act, was effective, future events affecting our business may cause us to significantly modify our disclosure controls and procedures.

Changes in Internal Control over Financial Reporting

In 2021, we implemented the first phase of our enterprise resource planning software, Microsoft Dynamics D365 ("Dynamics"), as part of a plan to integrate and upgrade our systems and processes. The implementation of this software is scheduled to continue in phases over a number of years as the Company grows and as we move towards commercialization of our initial product candidate, B-VEC. As the phased implementation of this system occurs, we expect certain changes to our processes and procedures which, in turn, will result in changes to our internal control over financial reporting. We expect Dynamics to continue to strengthen our internal financial controls. Management will continue to evaluate and monitor our internal controls as processes and procedures in each of the affected areas evolve. As we are still in the process of implementing these additional phases, no change in our internal control over financial reporting occurred during the year ended December 31, 2022.

Other than as discussed above, there was no change in our internal control over financial reporting identified in connection with the evaluation required by Rules 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the year ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Krystal Biotech, Inc.:

Opinion on Internal Control Over Financial Reporting

We have audited Krystal Biotech, Inc. and subsidiaries' (the Company) internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheet of the Company as of December 31, 2022 the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for the year ended December 31, 2022, and the related notes (collectively, the consolidated financial statements), and our report dated February 27, 2023 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit

preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ KPMG LLP

Pittsburgh, Pennsylvania
February 27, 2023

Item 9B. Other Information.

None

Item 9C. Disclosure Regarding Foreign Jurisdictions That Prevent Inspections.

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.
Information required by this Item is hereby incorporated by reference to our 2023 Definitive Proxy Statement, which will be filed prior to April 30, 2023..

Item 11. Executive Compensation.
Information required by this Item is hereby incorporated by reference to our 2023 Definitive Proxy Statement, which will be filed prior to April 30, 2023..

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.
Information required by this Item is hereby incorporated by reference to our 2023 Definitive Proxy Statement, which will be filed prior to April 30, 2023..

Item 13. Certain Relationships and Related Transactions, and Director Independence.
Information required by this Item is hereby incorporated by reference to our 2023 Definitive Proxy Statement, which will be filed prior to April 30, 2023..

Item 14. Principal Accounting Fees and Services.
Information required by this Item is hereby incorporated by reference to our 2023 Definitive Proxy Statement, which will be filed prior to April 30, 2023..

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) List the following documents filed as a part of the report:

(1) Financial statements

The response to this portion of Item 15 is set forth under Item 8 above.

(2) Financial statement schedule.

All schedules have been omitted because they are not required or because the required information is given in the financial statements or notes thereto set forth under Item 8 above.

(3) Exhibits.

A list of exhibits filed with this report or incorporated herein by reference can be found in the Exhibit Index of this Report.

Exhibit Index

Exhibit Number	Description
3.1	Second Amended and Restated Certificate of Incorporation of Krystal Biotech, Inc. (incorporated by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K, as filed with the SEC on September 25, 2017)
3.2	Amended and Restated Bylaws of Krystal Biotech, Inc. (incorporate by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K, as filed with the SEC on September 25, 2017)
4.1	Form of Common Stock Certificate (incorporated by reference to Exhibit 4.1 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)
4.2	Form of Indenture (including form of Debt Securities) (incorporated by reference to Exhibit 4.5 to the Company's Registration Statement on Form S-3 (Reg. No. 333-227632), as filed with the SEC on October 1, 2018)
4.3*	Description of Common Stock
10.1#	Indemnification Agreement by and between Krystal Biotech, Inc. and each of its directors and executive officers (incorporated by reference to Exhibit 10.1 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)
10.2#	Executive Employment Agreement, effective July 1, 2017, by and between Krystal Biotech, Inc. and Krish S. Krishnan (incorporated by reference to Exhibit 10.2 to the Company's Amendment No. 1 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 7, 2017)
10.3#	Executive Employment Agreement, effective May 1, 2017, by and between Krystal Biotech, Inc. and Suma M. Krishnan (incorporated by reference to Exhibit 10.3 to the Company's Amendment No. 1 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 7, 2017)
10.4#	Executive Employment Agreement, effective January 20, 2020, by and between Krystal Biotech, Inc. and Kathryn A. Romano (incorporated by reference to Exhibit 10.4 to the Company's Annual Report on Form 10-K, as filed with the SEC on March 1, 2021)
10.5#	Executive Employment Agreement, effective May 3, 2021 by and between Krystal Biotech, Inc. and Andy Orth
10.6#	Krystal Biotech, Inc. 2017 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)

Exhibit Number	Description
10.7#	Krystal Biotech, Inc. 2017 IPO Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)
10.8#	Form of Krystal Biotech, Inc. 2017 Stock Incentive Plan Notice of Stock Option Award (incorporated by reference to Exhibit 10.8 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)
10.9#	Form of Krystal Biotech, Inc. 2017 IPO Stock Incentive Plan Notice of Stock Option Award (incorporated by reference to Exhibit 10.9 to the Company's Amendment No. 2 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 14, 2017)
10.10	Lease Agreement, dated as of May 26, 2016, by and between Wharton Lender Associates, L.P. and Krystal Biotech, LLC (incorporated by reference to Exhibit 10.10 to the Company's Amendment No. 1 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 7, 2017)
10.11	Second Amendment to Lease Agreement, dated as of February 27, 2017, by and between Wharton Lender Associates, L.P. and Krystal Biotech, LLC (incorporated by reference to Exhibit 10.11 to the Company's Amendment No. 1 to the Company's Registration Statement on Form S-1 (Reg. No. 333-220085), as filed with the SEC on September 7, 2017)
10.12	Investors' Rights Agreement, dated as of August 7, 2017, by and among Krystal Biotech, Inc. and the investors listed on Schedule A thereto (incorporated by reference to Exhibit 10.9 to Form S-1 (Reg. No. 333-220085), as filed with the SEC on August 21, 2017)
10.13	Third amendment to Lease Agreement, dated as of May 31, 2018, by and between Wharton Lender Associate, L.P. and Krystal Biotech, Inc. (incorporated by reference to Exhibit 10.13 to the Company's Annual Report on Form 10-K, as filed with the SEC on March 1, 2021)
10.14	Fourth amendment to Lease Agreement, dated as of October 22, 2018, by and between Wharton Lender Associate, L.P. and Krystal Biotech, Inc. (incorporated by reference to Exhibit 10.14 to the Company's Annual Report on Form 10-K, as filed with the SEC on March 1, 2021)
10.15	Fifth amendment to Lease Agreement, dated as of December 10, 2018, by and between Wharton Lender Associate, L.P. and Krystal Biotech, Inc. (incorporated by reference to Exhibit 10.15 to the Company's Annual Report on Form 10-K, as filed with the SEC on March 1, 2021)
10.16	Sixth amendment to Lease Agreement and first amendment to storage space agreement, dated as of January 13, 2021, by and between Wharton Lender Associates, L.P. and Krystal Biotech, Inc.
10.17	Seventh amendment to Lease Agreement, dated as of May 11, 2021, by and between Wharton Lender Associates, L.P. and Krystal Biotech, Inc.
10.18	Eighth amendment to Lease Agreement, dated as of July 21, 2021, by and between Wharton Lender Associates, L.P. and Krystal Biotech, Inc.
10.19	Ninth amendment to Lease Agreement, dated as of January 4, 2022, by and between Wharton Lender Associates, L.P. and Krystal Biotech, Inc.
10.20	Purchase and Sale Agreement, dated January 29, 2021, by and between Krystal Biotech, Inc. and Northfield I, LLC. (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed with the SEC on February 2, 2021)
10.21	Standard Form of Contract for Construction and the corresponding General Conditions of the Contract for Construction with The Whiting-Turner Contracting Company, dated June 30, 2021 (incorporated by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, as filed with the SEC on August 9, 2021)
10.22	Guaranteed Maximum Price Amendment to Standard Form of Contract for Construction and the corresponding General Conditions of the Contract for Construction with The Whiting-Turner Contracting Company dated September 13, 2021 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, as filed with the SEC on September 16, 2021)
10.23*#	Form of Krystal Biotech, Inc. 2017 IPO Stock Incentive Plan Notice of Restricted Stock Award and Restricted Stock Award Agreement

16.1	Letter to Securities and Exchange Commission from Mayer Hoffman McCann P.C. dated May 26, 2022 (incorporated by reference to Exhibit 16.1 to the Company's Current Report on Form 8-K, as filed with the SEC on May 26, 2022).
21.1*	Subsidiaries of Krystal Biotech, Inc.
23.1*	Consent of KPMG LLP
23.2*	Consent of Mayer Hoffman McCann P.C.
31.1*	Certification of Periodic Report by Chief Executive Officer under Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Periodic Report by Chief Accounting Officer under Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*	Certification of Chief Executive Officer and Chief Accounting Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	(i) XBRL Instance Document, (ii) XBRL Taxonomy Extension Schema Document, (iii) XBRL Taxonomy Extension Calculation Linkbase Document, (iv) XBRL Taxonomy Extension Definition Linkbase Document, (v) XBRL Taxonomy Extension Label Linkbase Document, (vi) XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101).

* Filed herewith.

# Indicates a management contract or compensatory plan or arrangement.

Item 16. Form 10-K Summary.

The Company has elected to not include a summary.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Pittsburgh, State of Pennsylvania, on February 27, 2023.

KRYSTAL BIOTECH, INC.

By: /s/ Krish S. Krishnan
Krish S. Krishnan
President and Chief Executive Officer

By: /s/ Kathryn A. Romano
Kathryn A. Romano
Chief Accounting Officer

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Krish S. Krishnan and/or Kathryn A. Romano as his or her true and lawful attorney-in-fact and agent, with the full power of substitution, for him or her and in his or her name, place or stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent, or their, his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Krish S. Krishnan Krish S. Krishnan	President and Chief Executive Officer and Director (Principal Executive Officer)	February 27, 2023
/s/ Kathryn A. Romano Kathryn A. Romano	Chief Accounting Officer (Principal Financial Officer)	February 27, 2023
/s/ Suma M. Krishnan Suma M. Krishnan	President, R&D and Director	February 27, 2023
/s/ Daniel S. Janney Daniel S. Janney	Director	February 27, 2023
/s/ Dino A. Rossi Dino A. Rossi	Director	February 27, 2023
/s/ Kirti Ganorkar Kirti Ganorkar	Director	February 27, 2023
/s/ Julian Gangolli Julian Gangolli	Director	February 27, 2023
/s/ Chris Mason Chris Mason	Director	February 27, 2023
/s/ E. Rand Sutherland E. Rand Sutherland	Director	February 27, 2023

DESCRIPTION OF COMMON STOCK

General

Our authorized capital stock consists of 80,000,000 shares of common stock, $0.00001 par value per share, and 20,000,000 shares of preferred stock, $0.00001 par value per share. Our common stock is registered under Section 12(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). We have no other securities registered under Section 12 of the Exchange Act.

The following description summarizes the most important terms of our common stock. Because it is only a summary, it does not contain all the information that may be important to you. The description is intended as a summary, and is qualified in its entirety by reference to our second amended and restated certificate of incorporation (our "Certificate of Incorporation") and our amended and restated bylaws (our "Bylaws"). For a complete description, you should refer to our Certificate of Incorporation and Bylaws.

Common Stock

Dividend Rights

The holders of our common stock are entitled to receive dividends out of funds legally available if our board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that our board of directors may determine.

Voting Rights

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders. We have not provided for cumulative voting for the election of directors in our Certificate of Incorporation. Accordingly, holders of a majority of the shares of our common stock will be able to elect all of our directors. Our Certificate of Incorporation has established a classified board of directors, divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms.

No Preemptive or Similar Rights

Our common stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions.

Right to Receive Liquidation Distributions

Upon our liquidation, dissolution or winding-up, the assets legally available for distribution to our stockholders would be distributable ratably among the holders of our common stock at that time, subject to prior satisfaction of all outstanding debt and liabilities.

Anti-Takeover Provisions

The provisions of Delaware law, our Certificate of Incorporation and our Bylaws could have the effect of delaying, deferring or discouraging another person from acquiring control of our company. These provisions, which are summarized below, may have the effect of discouraging takeover bids. They are also designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate with an unfriendly or unsolicited acquirer outweigh the disadvantages of discouraging a proposal to acquire us because negotiation of these proposals could result in an improvement of their terms.

Delaware Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law (the "DGCL"), regulating corporate takeovers. In general, Section 203 of the DGCL prohibits a publicly held Delaware corporation from engaging in a business combination with an interested stockholder for a period of three years following the date on which the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or 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, but not the outstanding voting stock owned by the interested stockholder: (i) shares owned by persons who are directors and also officers; and (ii) shares owned by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66.67% of the outstanding voting stock that is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction or series of transactions together resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation's outstanding voting stock. We expect the existence of this provision to have an anti-takeover effect with respect to transactions our board of directors does not approve in advance. We also anticipate that Section 203 of the DGCL may also discourage attempts that might result in a premium over the market price for the shares of common stock held by stockholders.

Second Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws Provisions

Our Certificate of Incorporation and our Bylaws include a number of provisions that could deter hostile takeovers or delay or prevent changes in control of our company, including the following:

- *Board of Directors Vacancies.* Our Certificate of Incorporation and Bylaws authorizes only our board of directors to fill vacant directorships, including newly created seats. In addition, the number of directors constituting our board of directors may only be set by a resolution adopted by a majority vote of our entire board of directors. These provisions would prevent a stockholder from increasing the size of our board of directors and then gaining control of our board of directors by filling the resulting vacancies with its own nominees. This makes it more difficult to change the composition of our board of directors but promotes continuity of management.

- *Classified Board*. Our Certificate of Incorporation and Bylaws provide that our board of directors will be classified into three classes of directors, each with staggered three-year terms. A third party may be discouraged from making a tender offer or otherwise attempting to obtain control of us as it is more difficult and time consuming for stockholders to replace a majority of the directors on a classified board of directors.

- *Stockholder Action; Special Meetings of Stockholders*. Our Certificate of Incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. As a result, a holder controlling a majority of our capital stock may not amend our restated bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our Certificate of Incorporation and Bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, or our Chief Executive Officer, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.

- *Advance Notice Requirements for Stockholder Proposals and Director Nominations*. Our Bylaws provides advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our Bylaws also specifies certain requirements regarding the form and content of a stockholder's notice. These provisions may preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

- *No Cumulative Voting*. The DGCL provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our Certificate of Incorporation does not provide for cumulative voting.

- *Directors Removed Only for Cause*. Our Certificate of Incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of the holders of at least two-thirds of our outstanding common stock.

- *Amendment of Charter Provisions*. Any amendment of the above expected provisions in our Certificate of Incorporation requires approval by holders of at least two-thirds of our outstanding common stock.

- *Issuance of Undesignated Preferred Stock*. Our board of directors has the authority, without further action by the stockholders, to issue up to 20,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock will enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or other means.

- *Choice of Forum*. Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our Certificate of Incorporation or our Bylaws; any action to interpret, apply, enforce or determine the validity of our Certificate of Incorporation or our Bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent's address is 150 Royall Street, Canton, MA 02021, and its telephone number is 1-800-962-4284. Our shares of common stock were issued in uncertificated form only, subject to limited circumstances.

NASDAQ Capital Market Listing

Our common stock is listed on The NASDAQ Capital Market under the symbol "KRYS."

KRYSTAL BIOTECH, INC. 2017 IPO STOCK INCENTIVE PLAN

NOTICE OF RESTRICTED STOCK BONUS AWARD

Grantee's Name and Address: __

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You (the "Grantee") have been granted shares of Common Stock of the Company (the "Award"), subject to the terms and conditions of this Notice of Restricted Stock Bonus Award (the "Notice"), the Krystal Biotech, Inc. 2017 IPO Stock Incentive Plan, as amended from time to time (the "Plan"), and the Restricted Stock Bonus Award Agreement (the "Agreement") attached hereto, as follows. Unless otherwise provided herein, the terms in this Notice shall have the same meaning as those defined in the Plan.

Award Number __

Date of Award

Vesting Commencement Date

Total Number of Shares of Common Stock Awarded (the "Shares") __

Vesting Schedule:

Subject to the Grantee's Continuous Service and other limitations set forth in this Notice, the Agreement and the Plan, the Shares will "vest" in accordance with the following schedule (the "Vesting Schedule"):

The unvested Award shall vest ratably over a four year period with one-fourth of the Award vesting on the Vesting Commencement Date and one-fourth vesting on each anniversary thereafter until all Shares have vested.

During any authorized leave of absence, the vesting of the Shares as provided in this schedule shall be suspended after the leave of absence exceeds a period of three (3) months. Vesting of the Shares shall resume upon the Grantee's termination of the leave of absence and return to service to the Company or a Related Entity. The Vesting Schedule of the Shares shall be extended by the length of the suspension.

In the event of the Grantee's change in status from Employee, Director or Consultant to any other status of Employee, Director or Consultant, the Shares shall continue to vest in accordance with the Vesting Schedule set forth above.

For purposes of this Notice and the Agreement, the term "vest" shall mean, with respect to any Shares, that such Shares are no longer subject to forfeiture to the Company. Shares that have not vested are deemed "Restricted Shares." If the Grantee would become vested in a fraction of a Restricted Share, such Restricted Share shall not vest until the Grantee becomes vested in the entire Share.

Vesting shall cease upon the date of termination of the Grantee's Continuous Service for any reason, including death or Disability. In the event the Grantee's Continuous Service is terminated for any reason, including death or Disability, any Restricted Shares held by the Grantee immediately following such termination of Continuous Service shall be deemed reconveyed to the Company and the Company shall thereafter be the legal and beneficial owner of the Restricted Shares and shall have all rights and interest in or related thereto without further action by the Grantee. The foregoing forfeiture provisions set forth in this Notice as to Restricted Shares shall apply to the new capital stock or other property (including cash paid other than as a regular cash dividend) received in exchange for the Shares in consummation of any transaction described in Section 11 of the Plan and such stock or property shall be

deemed Additional Securities (as defined in the Agreement) for purposes of the Agreement, but only to the extent the Shares are at the time covered by such forfeiture provisions.

The Award shall be subject to the provisions of Section 11 of the Plan in the event of a Corporate Transaction or Change in Control.

IN WITNESS WHEREOF, the Company and the Grantee have executed this Notice and agree that the Award is to be governed by the terms and conditions of this Notice, the Plan and the Agreement.

Krystal Biotech, Inc.,
a Delaware corporation

By: __
Title: __

THE GRANTEE ACKNOWLEDGES AND AGREES THAT THE SHARES SHALL VEST, IF AT ALL, ONLY DURING THE PERIOD OF THE GRANTEE'S CONTINUOUS SERVICE OR AS OTHERWISE SPECIFICALLY PROVIDED HEREIN (NOT THROUGH THE ACT OF BEING HIRED, BEING GRANTED THIS AWARD OR ACQUIRING SHARES HEREUNDER). The GRANTEE FURTHER ACKNOWLEDGES AND AGREES THAT NOTHING IN THIS NOTICE, THE AGREEMENT, OR THE PLAN SHALL CONFER UPON THE GRANTEE ANY RIGHT WITH RESPECT TO FUTURE AWARDS OR CONTINUATION OF THE GRANTEE'S CONTINUOUS SERVICE, NOR SHALL IT INTERFERE IN ANY WAY WITH THE GRANTEE'S RIGHT OR THE RIGHT OF THE COMPANY OR RELATED ENTITY TO WHICH THE GRANTEE PROVIDES SERVICES TO TERMINATE THE GRANTEE'S CONTINUOUS SERVICE AT ANY TIME, WITH OR WITHOUT CAUSE, AND WITH OR WITHOUT NOTICE. THE GRANTEE ACKNOWLEDGES THAT UNLESS THE GRANTEE HAS A WRITTEN EMPLOYMENT AGREEMENT WITH THE COMPANY TO THE CONTRARY, THE GRANTEE'S STATUS IS AT WILL.

The Grantee acknowledges receipt of a copy of the Plan and the Agreement and represents that he or she is familiar with the terms and provisions thereof, and hereby accepts the Award subject to all of the terms and provisions hereof and thereof. The Grantee has reviewed this Notice, the Agreement and the Plan in their entirety, has had an opportunity to obtain the advice of counsel prior to executing this Notice and fully understands all provisions of this Notice, the Agreement and the Plan. The Grantee hereby agrees that all questions of interpretation and administration relating to this Notice, the Plan and the Agreement shall be resolved by the Administrator in accordance with Section 12 of the Agreement. The Grantee further agrees to the venue selection and waiver of a jury trial in accordance with Section 13 of the Agreement. The Grantee further agrees to notify the Company upon any change in the residence address indicated in this Notice.

The Grantee further acknowledges that, from time to time, the Company may be in a "blackout period" and/or subject to applicable federal securities laws that could subject the Grantee to liability for engaging in any transaction involving the sale of the Shares. The Grantee further acknowledges and agrees that, prior to the sale of any Shares acquired under the Award, it is the Grantee's responsibility to determine whether or not the sale of the Shares will subject the Grantee to liability under insider trading rules or other applicable federal securities laws.

The Company may, in its sole discretion, decide to deliver this Notice, the Agreement, the Plan and the Plan prospectus (collectively, the "Plan Documents") to the Grantee by electronic means or request the Grantee's consent to participate in the Plan by electronic means. The Grantee hereby agrees to Company's provision to the Grantee of these documents by electronic delivery and agrees to participate in the Plan through an on-line or electronic system established and maintained by the Company or a third party designated by the Company.

The Grantee acknowledges that the Grantee has access to the Company's intranet and has either received electronic or paper copies of the Plan Documents.

Dated: __ Signed: __

KRYSTAL BIOTECH, INC. 2017 IPO STOCK INCENTIVE PLAN

RESTRICTED STOCK BONUS AWARD AGREEMENT

1. Issuance of Shares. Krystal Biotech, Inc., a Delaware corporation (the "Company"), hereby issues to the Grantee (the "Grantee") named in the Notice of Restricted Stock Bonus Award (the "Notice"), the Total Number of Shares of Common Stock Awarded set forth in the Notice (the "Shares"), subject to the Notice, this Restricted Stock Bonus Award Agreement (the "Agreement") and the terms and provisions of the Company's 2017 IPO Stock Incentive Plan (the "Plan"), as amended from time to time, which are incorporated herein by reference. Unless otherwise defined herein, the terms defined in the Plan shall have the same defined meanings in this Agreement. All Shares issued hereunder will be deemed issued to the Grantee as fully paid and nonassessable shares, and the Grantee will have the right to vote the Shares at meetings of the Company's stockholders. The Company shall pay any applicable stock transfer taxes imposed upon the issuance of the Shares to the Grantee hereunder.

2. Transfer Restrictions. The Shares issued to the Grantee hereunder may not be sold, transferred by gift, pledged, hypothecated, or otherwise transferred or disposed of by the Grantee prior to the date when the Shares become vested pursuant to the Vesting Schedule set forth in the Notice. Any attempt to transfer Restricted Shares in violation of this Section 2 will be null and void and will be disregarded.

3. Escrow of Stock. For purposes of facilitating the enforcement of the provisions of this Agreement, the Grantee agrees, immediately upon receipt of the certificate(s) for the Restricted Shares, to deliver such certificate(s), together with a Stock Assignment in the form attached hereto as Exhibit A, executed in blank by the Grantee with respect to each such stock certificate, to the Secretary or Assistant Secretary of the Company, or their designee, to hold in escrow for so long as such Restricted Shares have not vested pursuant to the Vesting Schedule set forth in the Notice, with the authority to take all such actions and to effectuate all such transfers and/or releases as may be necessary or appropriate to accomplish the objectives of this Agreement in accordance with the terms hereof. The Grantee hereby acknowledges that the appointment of the Secretary or Assistant Secretary of the Company (or their designee) as the escrow holder hereunder with the stated authorities is a material inducement to the Company to make this Agreement and that such appointment is coupled with an interest and is accordingly irrevocable. The Grantee agrees that the Restricted Shares may be held electronically in a book entry system maintained by the Company's transfer agent or other third party and that all the terms and conditions of this Section 3 applicable to certificated Restricted Shares will apply with the same force and effect to such electronic method for holding the Restricted Shares. The Grantee agrees that such escrow holder shall not be liable to any party hereto (or to any other party) for any actions or omissions unless such escrow holder is grossly negligent relative thereto. The escrow holder may rely upon any letter, notice or other document executed by any signature purported to be genuine and may resign at any time. Upon the vesting of Restricted Shares, the escrow holder will, without further order or instruction, transmit to the Grantee the certificate evidencing such Shares; *provided*, *however*, that no transmittal of certificates evidencing the Shares will occur unless and until the Grantee has satisfied all Tax Withholding Obligations (as defined in Section 5(c) below).

4. Additional Securities and Distributions.

(a) Any securities or cash received (other than a regular cash dividend) as the result of ownership of the Restricted Shares (the "Additional Securities"), including, but not by way of limitation, warrants, options and securities received as a stock dividend or stock split, or as a result of a recapitalization or reorganization or other similar change in the Company's capital structure, shall be retained in escrow in the same manner and subject to the same conditions and restrictions as the Restricted Shares with respect to which they were issued, including, without limitation, the Vesting Schedule set forth in the Notice. The Grantee shall be entitled to direct the Company to exercise any warrant or option received as Additional Securities upon supplying the funds necessary to do so, in which event the securities so purchased shall constitute Additional Securities, but the Grantee may not direct the Company to sell any such warrant or option. If Additional Securities consist of a convertible security, the Grantee may exercise any conversion right, and any securities so acquired shall constitute Additional Securities. In the event of any change in certificates evidencing the Shares or the Additional Securities by reason of any recapitalization, reorganization or other transaction that results in the creation of Additional Securities, the escrow holder is authorized to deliver to the issuer the certificates evidencing the Shares or the Additional Securities in exchange for the certificates of the replacement securities.

(b) The Company shall disburse to the Grantee all regular cash dividends with respect to the Shares and Additional Securities (whether vested or not), less any applicable withholding obligations.

5. Taxes.

(a) Section 83(b) Election and Withholding of Taxes. The Grantee shall provide the Administrator with a copy of any timely election made pursuant to Section 83(b) of the Internal Revenue Code or similar provision of state law (collectively, an "83(b) Election"), a form of which is attached hereto as Exhibit B. If the Grantee makes a timely 83(b) Election, the Grantee shall immediately pay the Company the amount necessary to satisfy any applicable foreign, federal, state, and local income and employment tax withholding obligations. If the Grantee does not make a timely 83(b) Election, the Grantee shall, as Shares shall vest or at the time withholding is otherwise required by any Applicable Law, pay the Company the amount necessary to satisfy any applicable foreign, federal, state, and local income and employment tax withholding obligations. The manners in which the Grantee may pay the Company the amount necessary to satisfy any applicable foreign, federal, state, and local income and employment tax withholding obligations are set forth in subsection (c) below. The Grantee hereby represents that he or she understands (a) the contents and requirements of the 83(b) Election, (b) the application of Section 83(b) to the receipt of the Shares by the Grantee pursuant to this Agreement, (c) the nature of the election to be made by the Grantee under Section 83(b), and (d) the effect and requirements of the 83(b) Election under relevant state and local tax laws. The Grantee further represents that he or she intends to file an election pursuant to Section 83(b) with the Internal Revenue Service within thirty (30) days following the date of this Agreement, and submit a copy of such election to the Company and with his or her federal tax return for the calendar year in which the date of this Agreement falls.

(b) Tax Liability. The Grantee is ultimately liable and responsible for all taxes owed by the Grantee in connection with the Award, regardless of any action the Company or any Related Entity takes with respect to any tax withholding obligations that arise in connection with the Award. Neither the Company nor any Related Entity makes any representation or undertaking regarding the treatment of any tax withholding in connection with the grant or vesting of the Award or the subsequent sale of Shares subject to the Award. The Company and its Related Entities do not commit and are under no obligation to structure the Award to reduce or eliminate the Grantee's tax liability.

(c) Payment of Withholding Taxes. Prior to any event in connection with the Award (e.g., upon the filing of an 83(b) Election or vesting) that the Company determines may result in any tax withholding obligation, whether United States federal, state, local or non-U.S., including any social insurance, employment tax, payment on account or other tax-related obligation (the "Tax Withholding Obligation"), the Grantee must arrange for the satisfaction of the minimum amount of such Tax Withholding Obligation in a manner acceptable to the Company.

(i) *By Share Withholding.* Notwithstanding Section 7(c) of the Plan, if permissible under Applicable Law, the Administrator may permit the Grantee to elect to authorize the Company to withhold from those Shares otherwise issuable to the Grantee the whole number of Shares sufficient to satisfy up to the maximum applicable Tax Withholding Obligation. The maximum applicable Tax Withholding Obligation is based on the applicable rates of the relevant tax authorities (for example, federal, state and local), including the Grantee's share of payroll or similar taxes, as provided in the tax law, regulations or the authority's administrative practices, not to exceed the highest statutory rate in that jurisdiction. Any elections to have Shares withheld or sold for this purpose will be made in accordance with the requirements established by the Administrator for such elections and be in writing in a form acceptable to the Administrator. Further, if permissible under Applicable Law, the Grantee hereby authorizes the Company to, upon the exercise of its sole discretion, withhold from those Shares otherwise issuable to the Grantee the whole number of Shares sufficient to satisfy the minimum applicable Tax Withholding Obligation. The Grantee acknowledges that the withheld Shares may still not be sufficient to satisfy the Grantee's minimum Tax Withholding Obligation. Accordingly, the Grantee agrees to pay to the Company or any Related Entity as soon as practicable, including through additional payroll withholding, any amount of the Tax Withholding Obligation that is not satisfied by the withholding of Shares described above.

(ii) *By Sale of Shares*. Unless the Grantee determines to satisfy the Tax Withholding Obligation by some other means in accordance with clause (iii) below, the Grantee's acceptance of this Award constitutes the Grantee's instruction and authorization to the Company and any brokerage firm determined acceptable to the Company for such purpose to, upon the exercise of Company's sole discretion, sell on the Grantee's behalf a whole number of Shares from those Shares issuable to the Grantee as the Company determines to be appropriate to generate cash proceeds sufficient to satisfy the minimum applicable Tax Withholding Obligation. Such Shares will be sold on the day such Tax Withholding Obligation arises (e.g., a vesting date) or as soon thereafter as practicable. The Grantee will be responsible for all broker's fees and other costs of sale, and the Grantee agrees to indemnify and hold the Company harmless from any losses, costs, damages, or expenses relating to any such sale. To the extent the proceeds of such sale exceed the Grantee's minimum Tax Withholding Obligation, the Company agrees to pay such excess in cash to the Grantee. The Grantee acknowledges that the Company or its designee is under no obligation to arrange for such sale at any particular price, and that the proceeds of any such sale may not be sufficient to satisfy the Grantee's minimum Tax Withholding Obligation. Accordingly, the Grantee agrees to pay to the Company or

any Related Entity as soon as practicable, including through additional payroll withholding, any amount of the Tax Withholding Obligation that is not satisfied by the sale of Shares described above.

(iii) *By Check, Wire Transfer or Other Means*. At any time not less than five (5) business days (or such fewer number of business days as determined by the Administrator) before any Tax Withholding Obligation arises (e.g., a vesting date), the Grantee may elect to satisfy the Grantee's Tax Withholding Obligation by delivering to the Company an amount that the Company determines is sufficient to satisfy the Tax Withholding Obligation by (x) wire transfer to such account as the Company may direct, (y) delivery of a certified check payable to the Company, or (z) such other means as specified from time to time by the Administrator.

Notwithstanding the foregoing, the Company or a Related Entity also may satisfy any Tax Withholding Obligation by offsetting any amounts (including, but not limited to, salary, bonus and severance payments) payable to the Grantee by the Company and/or a Related Entity. Furthermore, in the event of any determination that the Company and/or a Related Entity has failed to withhold a sum sufficient to pay all withholding taxes due in connection with the Award, the Grantee agrees to pay the Company and/or the Related Entity the amount of such deficiency in cash within five (5) days after receiving a written demand from the Company and/or the Related Entity to do so, whether or not the Grantee is an employee of the Company and/or the Related Entity at that time.

6. Stop-Transfer Notices. In order to ensure compliance with the restrictions on transfer set forth in this Agreement, the Notice or the Plan, the Company may issue appropriate "stop transfer" instructions to its transfer agent, if any, and, if the Company transfers its own securities, it may make appropriate notations to the same effect in its own records. The Company may issue a "stop transfer" instruction if the Grantee fails to satisfy any Tax Withholding Obligations.

7. Refusal to Transfer. The Company shall not be required (i) to transfer on its books any Shares that have been sold or otherwise transferred in violation of any of the provisions of this Agreement or (ii) to treat as owner of such Shares or to accord the right to vote or pay dividends to any purchaser or other transferee to whom such Shares shall have been so transferred.

8. Restrictive Legends. The Grantee understands and agrees that the Company shall cause the legends set forth below or legends substantially equivalent thereto, to be placed upon any certificate(s) evidencing ownership of the Shares together with any other legends that may be required by the Company or by state or federal securities laws:

THE SHARES REPRESENTED BY THIS CERTIFICATE ARE RESTRICTED BY THE TERMS OF THAT CERTAIN RESTRICTED STOCK BONUS AWARD AGREEMENT BETWEEN THE COMPANY AND THE NAMED STOCKHOLDER. The SHARES REPRESENTED BY THIS CERTIFICATE MAY BE TRANSFERRED ONLY IN ACCORDANCE WITH SUCH AGREEMENT, A COPY OF WHICH IS ON FILE WITH THE SECRETARY OF THE COMPANY.

9. Lock-Up Agreement.

(a) Agreement. The Grantee, if requested by the Company and the lead underwriter of any public offering of the Common Stock (the "Lead Underwriter"), hereby irrevocably agrees not to sell, contract to sell, grant any option to purchase, transfer the economic risk of ownership in, make any short sale of, pledge or otherwise transfer or dispose of any interest in any Common Stock or any securities convertible into or exchangeable or exercisable for or any other rights to purchase or acquire Common Stock (except Common Stock included in the public offering or acquired on the public market after the offering) during the 180-day period following the effective date of a registration statement of the Company filed under the Securities Act of 1933, as amended, or any shorter or longer period of time as the Lead Underwriter will specify. The Grantee further agrees to sign all documents as may be requested by the Lead Underwriter to effect the foregoing and agrees that the Company may impose stop-transfer instructions with respect to the Common Stock subject to the lock-up period until the end of the period. The Company and the Grantee acknowledge that each Lead Underwriter of a public offering of the Company's stock, during the period of the offering and for the lock-up period thereafter, is an intended beneficiary of this Section 9.

(b) No Amendment Without Consent of Underwriter. During the period from identification of a Lead Underwriter in connection with any public offering of the Company's Common Stock until the earlier of (i) the expiration of the lock-up period specified in Section 9(a) in connection with the offering or (ii) the abandonment of the offering by the Company and the Lead Underwriter, the provisions of this Section 9 may not be amended or waived except with the consent of the Lead Underwriter.

10. Entire Agreement: Governing Law. The Notice, the Plan and this Agreement constitute the entire agreement of the parties with respect to the subject matter hereof and supersede in their entirety all prior undertakings and agreements of the Company and the Grantee with respect to the subject matter hereof, and may not be modified adversely to the Grantee's interest except by means of a writing signed by the Company and the Grantee. These agreements are to be construed in accordance with and governed by the internal laws of the State of Delaware without giving effect to any choice of law rule that would cause the application of the laws of any jurisdiction other than the internal laws of the State of Delaware to the rights and duties of the parties. Should any provision of the Notice or this Agreement be determined to be illegal or unenforceable, the other provisions shall nevertheless remain effective and shall remain enforceable.

11. Construction. The captions used in the Notice and this Agreement are inserted for convenience and shall not be deemed a part of the Award for construction or interpretation. Except when otherwise indicated by the context, the singular shall include the plural and the plural shall include the singular. Use of the term "or" is not intended to be exclusive, unless the context clearly requires otherwise.

12. Administration and Interpretation. Any question or dispute regarding the administration or interpretation of the Notice, the Plan or this Agreement shall be submitted by the Grantee or by the Company to the Administrator. The resolution of such question or dispute by the Administrator shall be final and binding on all persons.

13. Venue and Waiver of Jury Trial. The parties agree that any suit, action, or proceeding arising out of or relating to the Notice, the Plan or this Agreement shall be brought in the United States District Court for Delaware (or should such court lack jurisdiction to hear such action, suit or proceeding, in a Delaware state court) and that the parties shall submit to the jurisdiction of such court. The parties irrevocably waive, to the fullest extent permitted by law, any objection the party may have to the laying of venue for any such suit, action or proceeding brought in such court. **THE PARTIES ALSO EXPRESSLY WAIVE ANY RIGHT THEY HAVE OR MAY HAVE TO A JURY TRIAL OF ANY SUCH SUIT, ACTION OR PROCEEDING.** If any one or more provisions of this Section 13 shall for any reason be held invalid or unenforceable, it is the specific intent of the parties that such provisions shall be modified to the minimum extent necessary to make it or its application valid and enforceable.

14. Notices. Any notice required or permitted hereunder shall be given in writing and shall be deemed effectively given upon personal delivery, upon deposit for delivery by an internationally recognized express mail courier service or upon deposit in the United States mail by certified mail (if the parties are within the United States), with postage and fees prepaid, addressed to the other party at its address as shown in these instruments, or to such other address as such party may designate in writing from time to time to the other party.

15. Language. If the Grantee has received this Agreement or any other document related to the Plan translated into a language other than English and if the translated version is different than the English version, the English version will control, unless otherwise prescribed by Applicable Law.

16. Nature of Award. In accepting the Award, the Grantee acknowledges and agrees that:

(a) the Plan is established voluntarily by the Company, it is discretionary in nature, and it may be modified, amended, suspended or terminated by the Company at any time, unless otherwise provided in the Plan and this Agreement;

(b) the Award is voluntary and occasional and does not create any contractual or other right to receive future awards, or benefits in lieu of awards, even if awards have been awarded repeatedly in the past;

(c) all decisions with respect to future awards, if any, will be at the sole discretion of the Company;

(d) the Grantee's participation in the Plan is voluntary;

(e) the Grantee's participation in the Plan shall not create a right to any employment with the Grantee's employer and shall not interfere with the ability of the Company or the employer to terminate the Grantee's employment relationship, if any, at any time;

(f) the Award is not part of normal or expected compensation or salary for any purposes, including, but not limited to, calculating any severance, resignation, termination, redundancy, end of service payments, bonuses, long-service awards, pension or retirement or welfare benefits or similar payments and in no event should be considered as compensation for, or relating in any way to, past services for the Company or any Related Entity;

(g) in the event that the Grantee is not an Employee of the Company or any Related Entity, the Award and the Grantee's participation in the Plan will not be interpreted to form an employment or service contract or relationship with the Company or any Related Entity;

(h) the future value of the underlying Shares is unknown and cannot be predicted with certainty;

(i) in consideration of the Award, no claim or entitlement to compensation or damages shall arise from termination of the Award or diminution in value of the Award or Shares acquired upon vesting of the Award, resulting from termination of the Grantee's Continuous Service by the Company or any Related Entity (for any reason whatsoever and whether or not in breach of local labor laws) and in consideration of the grant of the Award, the Grantee irrevocably releases the Company and any Related Entity from any such claim that may arise; if, notwithstanding the foregoing, any such claim is found by a court of competent jurisdiction to have arisen, then, by signing the Notice, the Grantee shall be deemed irrevocably to have waived his or her right to pursue or seek remedy for any such claim or entitlement;

(j) in the event of termination of the Grantee's Continuous Service (whether or not in breach of local labor laws), the Grantee's right to receive Awards under the Plan and to vest in such Awards, if any, will (except as otherwise provided in the Notice or herein) terminate effective as of the date that the Grantee is no longer providing services and will not be extended by any notice period mandated under local law (e.g., providing services would not include a period of "garden leave" or similar period pursuant to local law); furthermore, in the event of termination of the Grantee's Continuous Service (whether or not in breach of local labor laws), the Administrator shall have the exclusive discretion to determine when the Grantee is no longer providing services for purposes of this Award;

(k) the Company is not providing any tax, legal or financial advice, nor is the Company making any recommendations regarding the Grantee's participation in the Plan or the Grantee's acquisition or sale of the underlying Shares; and

(l) the Grantee is hereby advised to consult with the Grantee's own personal tax, legal and financial advisers regarding the Grantee's participation in the Plan before taking any action related to the Plan.

17. Data Privacy.

(a) *The Grantee hereby explicitly and unambiguously consents to the collection, use and transfer, in electronic or other form, of the Grantee's personal data as described in the Notice and this Agreement by and among, as applicable, the Grantee's employer, the Company and any Related Entity for the exclusive purpose of implementing, administering and managing the Grantee's participation in the Plan.*

(b) *The Grantee understands that the Company and the Grantee's employer may hold certain personal information about the Grantee, including, but not limited to, the Grantee's name, home address and telephone number, date of birth, social insurance or other identification number, salary, nationality, job title, any Shares or directorships held in the Company, details of all Awards or any other entitlement to Shares awarded, canceled, vested, unvested or outstanding in the Grantee's favor, for the exclusive purpose of implementing, administering and managing the Plan ("Data").*

(c) The Grantee understands that Data will be transferred to any third party assisting the Company with the implementation, administration and management of the Plan. The Grantee understands that the recipients of the Data may be located in the Grantee's country, or elsewhere, and that the recipients' country may have different data privacy laws and protections than the Grantee's country. The Grantee understands that the Grantee may request a list with the names and addresses of any potential recipients of the Data by contacting the Grantee's local human resources representative. The Grantee authorizes the Company and any other possible recipients which may assist the Company (presently or in the future) with implementing, administering and managing the Plan to receive, possess, use, retain and transfer the Data, in electronic or other form, for the sole purpose of implementing, administering and managing the Grantee's participation in the Plan. The Grantee understands that Data will be held only as long as is necessary to implement, administer and manage the Grantee's participation in the Plan. The Grantee understands that the Grantee may, at any time, view Data, request additional information about the storage and processing of Data, require any necessary amendments to Data or refuse or withdraw the consents herein, in any case without cost, by contacting in writing the Grantee's local human resources representative. The Grantee understands, however, that refusal or withdrawal of consent may affect the Grantee's ability to participate in the

Plan. For more information on the consequences of the Grantee's refusal to consent or withdrawal of consent, the Grantee understands that the Grantee may contact the Grantee's local human resources representative.

END OF AGREEMENT

EXHIBIT A

STOCK ASSIGNMENT

FOR VALUE RECEIVED, hereby sells, assigns and transfers unto [●], ( ) shares of the Common Stock of Krystal Biotech, Inc., a Delaware corporation (the "Company"), standing in his/her name on the books of the Company [represented by Certificate No. herewith] and does hereby irrevocably constitute and appoint the Secretary of the Company attorney to transfer the said stock in the books of the Company with full power of substitution.

DATED: __ __

Please sign this document but do not date it. The date and information of the transferee will be completed if and when the shares are assigned.

EXHIBIT B

ELECTION UNDER SECTION 83(b)
OF THE INTERNAL REVENUE CODE OF 1986

The undersigned taxpayer hereby elects, pursuant to the Internal Revenue Code, to include in gross income for _____ the amount of any compensation taxable in connection with the taxpayer's receipt of the property described below:

1. The name, address, taxpayer identification number and taxable year of the undersigned are:

TAXPAYER'S NAME:

TAXPAYER'S SOCIAL SECURITY NO.:

TAXABLE YEAR: Calendar Year _____

ADDRESS:

2. The property which is the subject of this election is _____ shares of the Common Stock of Krystal Biotech, Inc.

3. The property was transferred to the undersigned on _____, ____.

4. The property is subject to the following restrictions: The property is subject to a repurchase right pursuant to which the issuer has the right to acquire the property at the original purchase price if for any reason taxpayer's employment or service with the issuer is terminated. The issuer's repurchase right lapses in a series of periodic installments.

5. The fair market value of the property at the time of transfer (determined without regard to any restriction other than a restriction which by its terms will never lapse) is: $_____ per share x _____ shares = $_____.

6. The undersigned paid $0 per share x _____ shares for the property transferred for a total of $_____.

The undersigned has submitted a copy of this statement to the person for whom the services were performed in connection with the undersigned's receipt of the above-described property. The undersigned taxpayer is the person performing the services in connection with the transfer of said property.

The undersigned will file this election with the Internal Revenue Service office to which he files his annual income tax return not later than 30 days after the date of transfer of the property. A copy of the election also will be furnished to the person for whom the services were performed. The undersigned understands that this election will also be effective as an election under _____ law.

Dated:

—

Taxpayer

Exhibit 21.1

Subsidiaries of Krystal Biotech, Inc.

We have omitted the subsidiaries which, considered in the aggregate, would not constitute a “significant subsidiary,” as defined in Rule 1-02(w) of Regulation S-X.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-237983) on Form S-3ASR and (Nos. 333-269539, 333-220589, 333-252351, 333-262825) on Form S-8 of our reports dated February 27, 2023, with respect to the consolidated financial statements of Krystal Biotech, Inc. and the effectiveness of internal control over financial reporting.

/s/ KPMG LLP

Pittsburgh, Pennsylvania
February 27, 2023

Exhibit 23.2

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statement on Form S-3-ASR (No. 333-237983) and Form S-8 (Nos. 333-269539, 333-220589, 333-252351, 333-262825) of our report dated February 28, 2022, with respect to the consolidated financial statements of Krystal Biotech, Inc. as of December 31, 2021 and for the years ended December 31, 2021 and 2020, included in this annual report on Form 10-K of Krystal Biotech, Inc. as of and for the year ended December 31, 2022.

/s/ Mayer Hoffman McCann P.C.

San Diego, California
February 27, 2023

Exhibit 31.1

CERTIFICATION 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, Krish S. Krishnan, certify that:

1. I have reviewed this Annual Report on Form 10-K of Krystal Biotech, 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 small business issuer as of, and for, the periods presented in this report;

4. The small business issuer'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 small business issuer 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 small business issuer, including its 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 small business issuer'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 small business issuer's internal control over financial reporting that occurred during the small business issuer's most recent fiscal quarter (the small business issuer's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the small business issuer's internal control over financial reporting; and

5. The small business issuer's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the small business issuer's auditors and the audit committee of the small business issuer'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 small business issuer'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 small business issuer's internal control over financial reporting.

Date: February 27, 2023 By: /s/ Krish S. Krishnan

Krish S. Krishnan
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION 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, Kathryn A. Romano, certify that:

1. I have reviewed this Annual Report on Form 10-K of Krystal Biotech, 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 small business issuer as of, and for, the periods presented in this report;

4. The small business issuer'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 small business issuer 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 small business issuer, including its 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 small business issuer'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 small business issuer's internal control over financial reporting that occurred during the small business issuer's most recent fiscal quarter (the small business issuer's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the small business issuer's internal control over financial reporting; and

5. The small business issuer's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the small business issuer's auditors and the audit committee of the small business issuer'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 small business issuer'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 small business issuer's internal control over financial reporting.

Date: February 27, 2023 By: /s/ Kathryn A. Romano

Kathryn A. Romano
Chief Accounting Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Krystal Biotech, Inc. (the "Company") on Form 10-K for the period ending December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: February 27, 2023 By: /s/ Krish S. Krishnan

Krish S. Krishnan
President and Chief Executive Officer
(Principal Executive Officer)

Date: February 27, 2023 By: /s/ Kathryn A. Romano

Kathryn A. Romano
Chief Accounting Officer
(Principal Financial and Accounting Officer)