Filed Pursuant to Rule 424(b)(5)
Registration Statement No. 333-237983

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Maximum Aggregate Offering Price	Amount of Registration Fee (1)(2)
Common Stock, par value $0.00001 per share	$150,000,000	$16,365.00

(1) In accordance with Rules 457(o) and 457(r) under the Securities Act of 1933, as amended, the registration fee was calculated based on the maximum aggregate offering price of $150.0 million of the securities offered by this prospectus supplement.

(2) In accordance with Rules 456(b) and 457(r) under the Securities Act, we initially deferred payment of the registration fee for Registration Statement No. 333-237983 filed on May 4, 2020.

PROSPECTUS SUPPLEMENT **(To prospectus dated May 4, 2020)**

$150,000,000

Krystal Biotech, Inc.

Common Stock

We have entered into a sales agreement with Cowen and Company, LLC, or Cowen, relating to the shares of our common stock offered by this prospectus supplement and the accompanying prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to $150.0 million, from time to time, through Cowen acting as our agent.

Our common stock is traded on The Nasdaq Capital Market, or the Nasdaq, under the symbol “KRYS.” On December 30, 2020, the last reported sale price of our common stock on the Nasdaq was $60.41, per share.

Sales of shares of our common stock, if any, under this prospectus supplement and the accompanying prospectus may be made in sales deemed to be “at-the-market” offerings, as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on the Nasdaq or any other trading market for our common stock. Cowen is not required to sell any specific amount of securities but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, on mutually agreed terms between Cowen and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to Cowen for sales of common stock pursuant to the sales agreement will be an amount equal to 3.0% of the gross proceeds of any shares of common stock sold under the sales agreement. See “Plan of Distribution” beginning on page S-13 for additional information regarding the compensation to be paid to Cowen. In connection with the sale of the shares our common stock on our behalf, Cowen will be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation of Cowen will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen with respect to certain liabilities, including liabilities under the Securities Act of 1933, as amended.

We are an “emerging growth company” under the applicable Securities and Exchange Commission rules and, as such, we have elected to comply with certain reduced public company reporting requirements for this prospectus supplement, the accompanying prospectus and future filings.

Our business and an investment in our common stock involves a high degree of risk. Please read “Risk Factors” beginning on page S-8 of this prospectus supplement and under similar headings in the documents incorporated by reference into this prospectus supplement concerning factors you should consider before investing in our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Cowen

December 31, 2020

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PROSPECTUS SUPPLEMENT

PROSPECTUS

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a "shelf" registration statement on Form S-3 (File No. 333-237983) that we filed with the Securities and Exchange Commission on May 4, 2020 and which became effective upon filing.

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part is the accompanying prospectus, which gives more general information about the shares of our common stock and other securities we may offer from time to time under our shelf registration statement, some of which does not apply to the securities offered by this prospectus supplement. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or any document incorporated by reference herein or therein, on the other hand, you should rely on the information in this prospectus supplement.

You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering before making an investment decision. You should also read and consider the information in the documents referred to in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Information Incorporated by Reference." Neither we nor Cowen have authorized any other person to provide you with any information that is different. If anyone provides you with different or inconsistent information, you should not rely on it. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the offering of shares of our common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement must inform themselves about, and observe any restrictions relating to, the offering of shares of our common stock and the distribution of this prospectus supplement outside the United States. This prospectus supplement does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

The information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering is accurate only as of its respective date, regardless of the time of delivery of the respective document or of any sale of securities covered by this prospectus supplement. You should not assume that the information contained in or incorporated by reference in this prospectus supplement or the accompanying prospectus, or in any free writing prospectus that we have authorized for use in connection with this offering, is accurate as of any date other than the respective dates thereof.

Unless the context indicates otherwise, as used in this prospectus supplement, the terms "Krystal," the "Company," "we," "us" and "our" refer to Krystal Biotech, Inc., a Delaware corporation, and its wholly-owned subsidiaries, Krystal Australia Pty Ltd, an Australian proprietary limited company, and Jeune, Inc., a Delaware corporation.

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement and the accompanying prospectus are the property of their respective owners.

PROSPECTUS SUPPLEMENT SUMMARY

The following summary highlights certain information about us, this offering and selected information contained elsewhere or incorporated by reference in this prospectus supplement. This summary does not contain all of the information you should consider before investing in our common stock. Before making an investment decision, you should carefully read the entire prospectus supplement and the accompanying prospectus (including the documents incorporated by reference herein and therein), especially the risks of investing in our common stock discussed under the heading "Risk Factors" in this prospectus supplement and the accompanying prospectus, our Annual Report on Form 10-K for the year ended December 31, 2019 and our Quarterly Report on Form 10-Q for the three months ended September 30, 2020, which are incorporated by reference into this prospectus supplement and the accompanying prospectus. You should also carefully read the information incorporated by reference into this prospectus supplement, including our financial statements, and the exhibits to the registration statement of which this prospectus supplement is a part.

In this prospectus supplement, unless we indicate otherwise or the context requires, references to the "Company," "Krystal," "we," "our," "ours," and "us" refer to Krystal Biotech, Inc. and its consolidated subsidiaries. The following summary is qualified in its entirety by the more detailed information and financial statements and notes thereto included elsewhere in this prospectus supplement.

Overview

We are a clinical stage gene therapy company developing a new class of transformative medicines to treat diseases caused by gene or protein dysfunction or absence. Using our patented platform that is based on engineered HSV-1, we create vectors that encode functional proteins. Our vector is designed to be specifically and efficiently delivered to the target cell in an outpatient setting, via topical or intradermal routes of administration, where the cell's own machinery transcribes and translates the encoded protein, restoring or augmenting protein function to treat or prevent disease.

Our Product Candidates

Beremagene Geperpavec ("B-VEC") for the treatment of Dystrophic Epidermolysis Bullosa

Our lead product candidate, B-VEC, is a topical gene therapy to treat dystrophic epidermolysis bullosa, or DEB, a rare and severe monogenic skin disease for which there is currently no approved treatment. 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, or COL7, that forms anchoring fibrils that bind the dermis, or inner layer of the skin, to the epidermis, or 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.

On July 28, 2020, we announced initiation of our Phase 3 pivotal trial known as GEM-3. The trial is 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 aims to enroll approximately thirty participants with DEB, aged six months or older at time of consent. Investigator identified wound pairs, up to three in each patient, are deemed the "primary"

wounds. These primary wounds will be treated once weekly for six months with either B-VEC or placebo, until wound closure. If a wound were to re-open at any point during the study, weekly dosage will resume until closure. The dose administered to each wound is dependent on the size of the wound and ranges from 4x10^8 to 1.2x10^9 PFU per wound. A maximum vector dose per patient per week has been defined on the basis of preclinical and clinical safety data. In the event that the maximum dose per patient has not been reached based on dosing of the primary wounds, the study investigators and patients will have the opportunity to select additional "secondary" wounds across which the remaining weekly dose may be applied.

The Primary Outcome Measure is complete wound healing determined by the Investigator, as compared to baseline in B-VEC treated wounds versus placebo treated wounds at Weeks 20, 22 and 24. Secondary endpoints to be evaluated in the study include complete wound healing at Weeks 8, 10 and 12; the mean change in pain severity (using either a VAS or FLACC-R Scale) per primary wound site associated with wound dressing; the proportion of primary wound sites with ³75% healing assessed via Canfield photography. Additional exploratory measures include relative time to wound closure from baseline, duration of wound closure, mean reduction in wound surface area in B-VEC treated versus placebo treated wounds, mean change in Quality of Life in addition to Skindex score as compared to baseline at Week 24. Throughout the study, participants will complete questionnaires, have images captured of their study wounds, undergo physical exams, have vital signs and safety labs monitored. We expect to complete enrollment in this study in early 2021 and anticipate having top-line data from this trial as well as filing of a Biologics License Application, or BLA, with the U.S. Food and Drug Administration, or FDA, in 2021. We are aligned with the European Medicines Agency, or EMA, on a pivotal trial design and we believe that data from GEM-3 will form the basis of a Marketing Authorisation Application, or MAA, filing shortly after the BLA.

In May 2020, complete Phase 1/2 data from the GEM-1 and GEM-2 studies was presented at the Society of Investigational Dermatology, or SID, meeting. The Phase 1 portion of the trial commenced 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.

The FDA and the 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, in 2019, the FDA granted Regenerative Medicine Advanced Therapy, or RMAT, to B-VEC for the treatment of DEB and the EMA granted PRIority MEdicines, or PRIME, eligibility for B-VEC to treat DEB. The PRIME designation is awarded by the EMA to promising medicines that target an unmet medical need.

KB105 for the treatment of Autosomal Recessive Congenital Ichthyosis ("ACRI")

Our second pipeline candidate, KB105, delivers functional human transglutaminase 1, or TGM1, genes using our gene therapy platform to patients with TGM1-deficient ARCI. 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 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 and trans-epidermal exposure to unwanted toxins and surface microorganisms, greatly increasing the risk of infection and sepsis. Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life. There are currently no treatments targeting molecular correction of this disease.

In August 2020, we initiated the second phase of our Phase 1/2 clinical trial of KB105 to treat ARCI. We have enrolled one patient in whom four rectangular 100cm2 (4-inch x 4-inch) areas of skin were selected as Target Areas. Two sites will receive an initial and a repeat dose of 4.0 x 10^9 PFU/Treated Area (TA) while the other two sites will receive 1.0 x 10^10 PFU/ TA. The primary objective of the study is to assess the improvement in localized severity of disease through an Investigator's Global Assessment ("IGA") of disease severity in the treatment area and TGM1 expression and activity and to evaluate safety through the incidence of adverse events associated with KB105 post administration.

KB301 for the treatment of aesthetic skin conditions

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, human dermal collagens (i.e., neocollagenesis), thereby correcting the molecular defect underlying the aged phenotype. We believe that our approach of directed expression of full-length human type 3 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 and other superficial skin defects.

We initiated the Phase 1 safety clinical trial for the treatment of wrinkles and acne scars on August 25, 2020. On October 8, 2020, we announced presentation of preclincial data supporting the ongoing development of KB301 at the American Society for Dermatologic Surgery ("ASDS") 2020 Virtual Meeting.

KB104 for the treatment of Netherton Syndrome

KB104 is designed to deliver functional Serine Protease Inhibitor Kazal-type 5 ("SPINK5"), genes using our gene therapy platform to patients suffering from Netherton Syndrome, which is a debilitating monogenic autosomal recessive skin disorder that causes defective keratinization, severe skin barrier defects, and recurrent infections. Severe Netherton Syndrome symptoms in infants are 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.

KB407 for the treatment of Cystic Fibrosis

Recognizing the breadth and potential transformative power of our HSV-1 vector platform, we have expanded the scope of our product development beyond skin and have begun preclinical efforts in pulmonary diseases. The large payload capacity, robust tropism to epithelial cells (including human airway epithelia), immune-evasive properties, and manufacturing scalability of our HSV-based vector platform gives us an advantage over other viral vector therapies for pulmonary indications. Our preclinical efforts to date have led to the development of a novel candidate, KB407, for the treatment of CF, which has been shown to successfully transduce human CF patient-derived epithelial cells and deliver functional cystic fibrosis transmembrane conductance regulator ("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 non-human primate study.

Based on feedback from regulatory agencies, Investigational New Drug ("IND") enabling safety and efficacy studies, including an additional safety study in non-human primates, are underway, and IND filing for KB407 is anticipated in 1H 2021. The FDA granted Orphan Drug Designation to KB407 on August 17, 2020, and Rare Pediatric Designation on September 28, 2020.

CF, the most common inherited genetic disorder in the United States, is caused by mutations in the gene encoding CFTR. Lack of functional CFTR 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 US 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 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.

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. On June 19, 2018, we incorporated Krystal Australia Pty Ltd, an Australian proprietary limited company, for the purposes of undertaking preclinical and clinical studies in Australia. On April 24, 2019, we incorporated Jeune, Inc. in Delaware, a wholly owned subsidiary, for the purposes of undertaking preclinical studies for aesthetic skin conditions. To date, our operations have been focused on organizing and staffing our company, developing our proprietary platform, identifying potential product candidates, undertaking preclinical studies and clinical trials, and developing our in-house cGMP facilities. Our website is located at http://www.krystalbio.com. We do not incorporate by reference into this prospectus the information on, or accessible through, our website.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of relief from certain reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- reduced obligations with respect to financial data, including presenting only two years of audited financial statements;
- an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act;
- reduced disclosure about our executive compensation arrangements in our periodic reports, proxy statements and registration statements; and
- exemptions from the requirements of holding non-binding advisory votes on executive compensation or golden parachute arrangements.

We may take advantage of these provisions for up to five years or such earlier time that we no longer qualify as an emerging growth company. We would cease to be an emerging growth company if

we have more than $1.07 billion in total annual gross revenues, qualify as a “large accelerated filer” as defined under the Exchange Act or issue more than $1.0 billion of non-convertible debt over a three-year period. We may choose to take advantage of some but not all of these reduced reporting burdens. For example, we intend to take advantage of the reduced reporting requirements with respect to disclosure regarding our executive compensation arrangements, have presented only two years of audited financial statements and only two years of related “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, and have taken advantage of the exemption from auditor attestation on the effectiveness of our internal controls over financial reporting. To the extent that we take advantage of these reduced reporting burdens, the information that we provide stockholders may be different than you might obtain from other public companies in which you hold equity interests.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a “smaller reporting company,” meaning that the market value of our stock held by non-affiliates is less than $700 million and our annual revenue was less than $100 million during our most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250 million or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. For so long as we remain a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure and other requirements that are applicable to other public companies that are not smaller reporting companies.

THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to $150.0 million.
Common stock to be outstanding immediately after this offering	Assuming all $150.0 million of shares of our common stock are sold in this offering at an assumed offering price of $60.41 per share, the last reported sale price of shares of our common stock on the Nasdaq on December 30, 2020, we would have had 22,189,902 shares of our common stock outstanding as of September 30, 2020.
Manner of offering	“At-the-market” offering that may be made from time to time through our sales agent, Cowen and Company, LLC. See “Plan of Distribution” on page S-13 of this prospectus supplement.
Use of proceeds	We currently intend to use the net proceeds from this offering, if any, together with our existing cash, cash equivalents and short-term investments: (i) to advance B-VEC through our Phase 3 clinical trial; (ii) to advance the clinical development of KB105 and KB301; (iii) to advance the pre-clinical and clinical development of KB104 and KB407; (iv) to complete development of a good manufacturing practices certified manufacturing facility for scale-up production of our pipeline compounds and commencement of operations of that facility; and (v) the balance for working capital and general corporate purposes, including research and development expenses and capital expenditures. See “Use of Proceeds” on page S-12 of this prospectus supplement.
Risk factors	Investing in our common stock involves significant risks. See “Risk Factors” on page S-8 of this prospectus supplement, and under similar headings in other documents incorporated by reference herein.
Nasdaq Capital Market Symbol	“KRYS”

The number of shares our common stock to be outstanding immediately after this offering is based on 19,706,870 shares our common stock outstanding as of September 30, 2020, and excludes, as of such date:

- 853,336 shares of our common stock issuable upon the exercise of outstanding stock options with a weighted-average exercise price of $39.93 per share; and

- 1,698,412 shares of our common stock reserved for future issuance under the Company's Stock Incentive Plan, as well as any automatic increases in the number of shares of common stock reserved for future issuance under this benefit plan.

Unless otherwise indicated, this prospectus supplement reflects and assumes no exercise of the outstanding options described above. To the extent options are exercised, new options are issued under our equity incentive plans, or we issue additional shares of common stock in the future, there may be further dilution to new investors.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risk factors described below, together with the risks under the heading "Risk Factors" beginning on page 14 of the accompanying prospectus and under Part I, Item IA of our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 10, 2020, and in our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2020 filed with the Securities and Exchange Commission on November 9, 2020, and all other information contained or incorporated by reference into this prospectus supplement and the accompanying prospectus, including our financial statements and the related notes, as updated by our subsequent filings under the Securities Exchange Act of 1934, as amended, and in any free writing prospectus that we have authorized for use in connection with this offering before acquiring any of our common stock. These risks could have a material and adverse impact on our business, results of operations, financial condition and growth prospects, which may cause the trading price of our common stock to decline and you could lose all or part of your investment.

Risks Related to This Offering and Ownership of our Common Stock

Our management will have broad discretion in the use of any proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of any proceeds from this offering and could spend the proceeds in ways that do not improve our business, financial condition or results of operations or enhance the value of our common stock. Our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds are being used appropriately. You may not agree with our decisions, and our use of the net proceeds may not yield any return on your investment. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our failure to apply any proceeds of this offering effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of these net proceeds. You will not have the opportunity to influence our decisions on how to use our net proceeds from this offering. The failure by our management to apply these funds effectively could result in financial losses that could harm our business, cause the price of our common stock to decline and delay the development of KB103, KB105, KB104, KB301, KB407 and any other product candidates we may develop. Pending their use, we may invest our cash, including the net proceeds from this offering, in a manner that does not produce income or that loses value. See "Use of Proceeds."

If you purchase our shares of our common stock in this offering, you will incur immediate and substantial dilution in the net tangible book value of your shares of our common stock.

The shares of our common stock sold in this offering from time to time will be sold at various prices; however, we expect that the public offering price of our common stock will be substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering and will suffer substantial dilution with respect to the net tangible book value of those shares of our common stock. Assuming that an aggregate of 2,483,032 shares of our common stock are sold at a public offering price of $60.41 per share, the last reported sale price of our common stock on the Nasdaq on December 30, 2020, for aggregate gross proceeds of approximately $150.0 million, and after deducting estimated commissions and offering expenses payable by us, you would incur immediate dilution of $40.26 per share, representing the difference between the assumed public offering price and our as adjusted net tangible book value per share of $20.15, as of September 30, 2020, after giving effect to this offering. Further, the future exercise of any options or warrants to purchase shares of our common stock and the vesting and settlement of any restricted stock units will result in additional dilution of your investment.

Future sales of shares of our common stock, or the perception that such sales may occur, could depress our share price, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market following this offering, or the perception by investors that our stockholders intend to sell substantial amounts of our common stock in the public market, could depress the market price of our common stock even if our business is doing well.

All of the shares sold in this offering, as well as shares issued upon the exercise of options granted to persons other than our officers and directors, are freely transferable without restrictions or further registration under the Securities Act. If our large stockholders, including our founders, or any of our other executive officers or directors were to sell a substantial portion of our common stock, or if the market perceived that any such stockholders or other executive officers or directors intends to sell shares of our common stock, such sale or perception could negatively affect our common stock price.

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

Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for biopharmaceutical or pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular 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:

- volatility resulting from the economic turmoil caused by the COVID-19 pandemic;
- our ability to successfully proceed to and conduct clinical trials;
- results of clinical trials of our product candidates or those of our competitors;
- 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 obtain or delays in obtaining 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; and
- general economic, industry and market conditions.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, as well as any free writing prospectus that we have authorized for use in connection with this offering, contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and releases issued by the Securities and Exchange Commission, the SEC, and within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements include, among others, information concerning our expectations, beliefs, strategy, future operations, future financial position, future revenue, projected expenses, business prospects, and plans and objectives of management. 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 forward-looking statements are based on our management’s current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. 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. Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled “Business,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” incorporated by reference from our most recent Annual Report on Form 10-K and in our Quarterly Reports on Form 10-Q, as well as any amendments thereto, filed with the SEC.

Forward-looking statements contained in this prospectus supplement include, but are not limited to, statements about the following:

- the initiation, timing, progress and results of preclinical and clinical trials for B-VEC, KB105, KB104, KB301, KB407 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 that the COVID-19 pandemic and measures to prevent its spread may have on our business operations, access to capital, research and development activities, and preclinical and clinical trials for B-VEC, KB105, KB104, KB301, KB407 and any other product candidates;
- the timing, scope or results of regulatory filings and approvals, including timing of final FDA or EMA approval, marketing and other regulatory approval of our product candidates;
- our ability to achieve certain accelerated or orphan drug designations from the FDA or EMA;
- our estimates regarding the potential market opportunity for B-VEC, KB105, KB104, KB301, KB407and any other product candidates;
- our research and development programs for our product candidates;
- our plans and ability to successfully develop and commercialize our product candidates, B-VEC, KB105, KB104, KB301, KB407 and our other 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 or obtain additional funding;
- our estimates regarding expenses, future revenue, 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;
- any statements regarding compliance with the listing standards of The NASDAQ Capital Market; and
- the impact of laws and regulations.

Forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in “Risk Factors” and elsewhere in this prospectus supplement and the accompanying prospectus. 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 prospectus supplement and/or the accompanying prospectus 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 prospectus supplement or the accompanying prospectus, as applicable. You should read this prospectus supplement, the accompanying prospectus, and the documents that we have filed as exhibits to the registration statement, of which this prospectus supplement is a part, 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.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sales proceeds of up to $150.0 million, from time to time, in this offering. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and net proceeds to us, if any, are not determinable at this time. There can be no assurance that, in the future, we will sell any shares under or fully utilize the sales agreement with Cowen as a source of financing.

We intend to use the net proceeds from this offering together with our existing cash, cash equivalents and short-term investments as follows:

- to advance our Phase 3 clinical trial of B-VEC;
- to advance the clinical development of KB105 and KB301;
- to advance the pre-clinical and clinical development of KB104 and KB407;
- to build out a good manufacturing practices certified manufacturing facility for scale-up production of our pipeline compounds and commencement of operations of that facility; and
- the balance for working capital and general corporate purposes, including research and development expenses and capital expenditures.

The expected net proceeds of this offering will not be sufficient for us to fund our product candidates through regulatory approval, and we will need to raise additional capital in order to complete the development and commercialization of our product candidates.

The amounts and timing of our use of the net proceeds from this offering will depend on a number of factors, including the timing and progress of our research and development efforts, the timing and progress of any partnering and commercialization efforts, technological advances and the competitive environment for our products, as well as the amount of cash used in our operations. Although we have no present intention or commitment to do so, we may use a portion of the net proceeds for the acquisition of, or investment in, technologies, intellectual property or businesses that complement our business.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the actual amounts that we will spend on the uses set forth above. We may find it necessary or advisable to use the net proceeds for other purposes, and our management will retain broad discretion over the allocation of the net proceeds of this offering. Pending the uses described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments or other investment-grade securities, certificates of deposits or short-term U.S. government securities.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen, under which we may issue and sell from time to time up to $150.0 million of our common stock through Cowen as our sales agent. Sales of our common stock, if any, will be made at market prices by any method that is deemed to be an “at the market” offering as defined in Rule 415 under the Securities Act, including sales made directly on the Nasdaq or any other trading market for our common stock. If authorized by us in writing, Cowen may purchase shares of our common stock as principal.

Cowen will offer our common stock subject to the terms and conditions of the sales agreement on a daily basis or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of common stock to be sold through Cowen on a daily basis or otherwise determine such maximum amount together with Cowen. Subject to the terms and conditions of the sales agreement, Cowen will use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us. We may instruct Cowen not to sell common stock if the sales cannot be effected at or above the price designated by us in any such instruction. Cowen or we may suspend the offering of our common stock being made through Cowen under the sales agreement upon proper notice to the other party. Cowen and we each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party’s sole discretion at any time.

The compensation to Cowen for sales of common stock pursuant to the sales agreement will be an amount equal to 3.0% of the gross proceeds of any shares of common stock sold under the sales agreement. We have also agreed to reimburse Cowen for up to $50,000 of Cowen’s actual outside legal expenses incurred by Cowen in connection with this offering and up to $10,000 of Cowen’s actual filing fees and associated legal expenses of Cowen’s outside counsel for filings with the FINRA Corporate Financing Department. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the sales agreement, will be approximately $200,000.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Cowen will provide written confirmation to us following the close of trading on the Nasdaq on each day in which common stock is sold through it as sales agent under the sales agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us.

We will report at least quarterly the number of shares of common stock sold through Cowen under the sales agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

Settlement for sales of common stock will occur, unless the parties agree otherwise, on the second business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sales of our common stock on our behalf, Cowen will be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation paid to Cowen will be deemed to be underwriting commissions or discounts. We have agreed in the sales agreement to provide indemnification and contribution to Cowen against certain liabilities, including liabilities under

the Securities Act of 1933, as amended. As sales agent, Cowen will not engage in any transactions that stabilizes our common stock.

Our common stock is listed on the Nasdaq and trades under the symbol “KRYS.” The transfer agent of our common stock is Computershare Trust Company, N.A.

Cowen and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

LEGAL MATTERS

The validity of the shares of our common stock being offered hereby will be passed upon by Morrison & Foerster LLP, San Francisco, California. Goodwin Procter LLP, New York, New York, is acting as counsel for Cowen in connection with certain legal matters related to this offering.

EXPERTS

Mayer Hoffman McCann P.C., an independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the years ended December 31, 2019 and 2018, as set forth in its report, which is incorporated by reference in this prospectus supplement. Our financial statements are incorporated by reference in reliance on Mayer Hoffman McCann P.C.'s report, given on the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 that we filed with the SEC. This prospectus supplement and the accompanying prospectus do not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus supplement and the accompanying prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Statements in this prospectus supplement concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to the filings. You should review the complete document to evaluate these statements.

Neither we nor any agent, underwriter or dealer has authorized any person to provide you with information that is different from that contained in this prospectus supplement and the accompanying prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We take no responsibility for and can provide no assurance as to the reliability of, any other information that others may give you. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus supplement and the accompanying prospectus is accurate as of any date other than the date on the front page of such documents, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of the securities offered by this prospectus supplement and the accompanying prospectus.

We are subject to the information requirements of the Exchange Act. In accordance with the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC, including us. The address of the SEC website is www.sec.gov.

We maintain a website at www.krystalbio.com. Copies of certain information filed by us with the SEC are also available on our website. Information contained in or accessible through our website does not constitute a part of this prospectus supplement or the accompanying prospectus and is not incorporated by reference into this prospectus supplement or the accompanying prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC rules allow us to "incorporate by reference" into this prospectus supplement information that we file with the SEC. Incorporation by reference allows us to disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference into this prospectus supplement is considered to be part of this prospectus supplement. These documents may include Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements. You should read the information incorporated by reference because it is an important part of this prospectus supplement.

This prospectus and the registration statement of which this prospectus is a part incorporate by reference the information or documents listed below, other than those documents or the portions of those documents deemed to be furnished and not filed in accordance with the SEC rules:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 filed with the SEC on March 10, 2020;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2020 filed with the SEC on May 4, 2020; our Quarterly Report on Form 10-Q for the fiscal quarter ended June 30, 2020 filed with the SEC on August 7, 2020; and our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2020 filed with the SEC on November 9, 2020;
- our Current Reports on Form 8-K filed with the SEC on February 25, 2020, May 5, 2020; May 13, 2020; May 21, 2020; June 1, 2020; and November 9, 2020;
- the sections of our Definitive Proxy Statement on Schedule 14A filed with the SEC on April 13, 2020, as supplemented on May 8, 2020, that are incorporated by reference to our Annual Report on Form 10-K for the fiscal year ended December 31, 2019; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on September 19, 2017, pursuant to Section 12(b) of the Exchange Act, including any amendment or report filed for the purpose of updating such description.

Any statement contained in any document incorporated by reference herein shall be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or any prospectus modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement.

We also incorporate by reference any future filings, other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items, made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, in each case, other than those documents or the portions of those documents deemed to be furnished and not filed in accordance with SEC rules, until the offering of the securities under the registration statement of which this prospectus supplement forms a part is terminated or completed. Information in such future filings updates and supplements the information provided in this prospectus supplement. Any statements in any such future filings will be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and later information filed with the SEC may update and supersede some of the information included or incorporated by reference in this prospectus supplement. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement or in any document previously incorporated by reference have been modified or superseded.

We will provide without charge to each person, including any beneficial owners, to whom this prospectus supplement is delivered, upon his or her written or oral request, a copy of any or all reports or documents referred to above which have been or may be incorporated by reference into this prospectus supplement but not delivered with this prospectus supplement, excluding exhibits to those reports or documents unless they are specifically incorporated by reference into those documents. You may request a copy of these documents by writing or telephoning us at the following address:

Krystal Biotech, Inc.
2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(412) 586-5830

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PROSPECTUS

Krystal Biotech, Inc.

Common Stock
Preferred Stock
Debt Securities
Warrants
Rights
Units

We may offer, from time to time, together or separately, in one or more offerings:

- common stock;
- preferred stock;
- debt securities;
- warrants to purchase common stock or preferred stock;
- rights to purchase common stock or preferred stock; and
- units comprised of two or more of the foregoing securities.

We may sell any combination of these securities in one or more offerings, in amounts, at prices and on terms to be determined at the time of each offering thereof. This prospectus provides you with a general description of the securities we may offer. Each time we offer securities using this prospectus, we will provide the specific terms of the securities and the offering in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add to, update or change the information contained in this prospectus and will also describe the specific manner in which we will offer the securities.

The securities may be sold directly by us to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section titled “Plan of Distribution” in this prospectus. If any agents, underwriters or dealers are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents, underwriters or dealers and any applicable fees, commissions, discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

This prospectus may not be used to sell any securities unless accompanied by a prospectus supplement. You should carefully read this prospectus, any accompanying prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference, prior to investing in any of our securities.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading “Risk Factors” beginning on page 14 of this prospectus, in any accompanying prospectus supplement and in any related free writing prospectus, and under similar headings in the documents incorporated by reference into this prospectus, any accompanying prospectus supplement and any related free writing prospectus.

Our common stock is traded on The NASDAQ Capital Market under the symbol “KRYS.” We do not expect our preferred stock, debt securities, warrants, rights or units to be listed on any securities exchange or over-the-counter market unless otherwise described in the applicable prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is May 4, 2020

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the U.S. Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf registration process, we may, from time to time, offer shares of our common stock, shares of our preferred stock, debt securities, warrants, rights or units comprised of two or more of the foregoing securities, together or separately, in one or more offerings.

This prospectus provides you with a general description of the securities we may offer. Each time we sell any securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that specific offering, including the specific amounts, prices and terms of the securities offered. Any prospectus supplement may include a discussion of risks or other special considerations applicable to us or the offered securities. Any prospectus supplement may also add to, update or change information contained in this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any prospectus supplement, on the other hand, you should rely on the information in the prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date-for example, a document incorporated by reference in the accompanying prospectus-the statement in the document having the later date modifies or supersedes the earlier statement.

This prospectus and any applicable prospectus supplement contain and incorporate by reference market data, industry statistics and other data that have been obtained or compiled from information made available by third parties. These data, to the extent they contain estimates or projections, involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates or projections. Industry publications and other reports we have obtained from independent parties generally state that the data contained in these publications or other reports have been obtained in good faith or from sources considered to be reliable, but they do not guarantee the accuracy or completeness of such data.

We urge you to carefully read this prospectus, any applicable prospectus supplement and any related free writing prospectus, any documents that we incorporate by reference in this prospectus, any applicable prospectus supplement and any related free writing prospectus, and the additional information described below under “Where You Can Find More Information” and “Incorporation of Certain Documents by Reference” before making an investment decision. You should rely only on the information contained or incorporated by reference in this prospectus, any applicable prospectus supplement and any related free writing prospectus. We have not authorized anyone to provide you with different information. If anyone provides you with additional, different or inconsistent information, you should not rely on it. You should not assume that the information we have included in this prospectus, any applicable prospectus supplement, any related free writing prospectus or any documents incorporated by reference herein or therein is accurate as of any date other than the dates of those documents. Our business, financial condition, results of operations and prospects may have changed since those dates.

This document may only be used where it is legal to sell these securities. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction whether the offer or sale is not permitted.

Unless the context indicates otherwise, as used in this prospectus, the terms “Krystal,” the “Company,” “we,” “us” and “our” refer to Krystal Biotech, Inc., a Delaware corporation, and its wholly-owned subsidiaries, Krystal Australia Pty Ltd, an Australian proprietary limited company, and Jeune, Inc., a Delaware corporation.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We are subject to the information requirements of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). In accordance with the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Such reports, proxy statements and other information filed by us are available to the public free of charge at www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at www.krystalbio.com. The information available on or through our website is not part of this prospectus or any accompanying prospectus supplement or related free writing prospectus and should not be relied upon.

This prospectus is part of a registration statement on Form S-3 that we filed with the SEC and does not contain all the information set forth or incorporated by reference in the registration statement. You should review the information and exhibits in the registration statement for further information about us and the securities being offered hereby. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to the filings. You should review the complete document to evaluate these statements.

INFORMATION INCORPORATED BY REFERENCE

The SEC rules allow us to "incorporate by reference" into this prospectus information that we file with the SEC. Incorporation by reference allows us to disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference into this prospectus is considered to be part of this prospectus. These documents may include Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements. You should read the information incorporated by reference because it is an important part of this prospectus.

This prospectus and the registration statement of which this prospectus is a part incorporate by reference the information or documents listed below, other than those documents or the portions of those documents deemed to be furnished and not filed in accordance with the SEC rules:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 filed with the SEC on March 10, 2020;
- our Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2020 filed with the SEC on May 4, 2020;
- our Current Report on Form 8-K filed with the SEC on February 25, 2020;
- the sections of our Definitive Proxy Statement on Schedule 14A filed with the SEC on April 15, 2020 that are incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2019; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on September 19, 2017, pursuant to Section 12(b) of the Exchange Act, including any amendment or report filed for the purpose of updating such description.

Any statement contained in any document incorporated by reference herein shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or any prospectus supplement modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We also incorporate by reference any future filings, other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items, made with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, in each case, other than those documents or the portions of those documents deemed to be furnished and not filed in accordance with SEC rules, until the offering of the securities under the registration statement of which this prospectus forms a part is terminated or completed. Information in such future filings updates and supplements the information provided in this prospectus. Any statements in any such future filings will be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and later information filed with the SEC may update and supersede some of the information included or incorporated by reference in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded.

We will provide without charge to each person, including any beneficial owners, to whom this prospectus is delivered, upon his or her written or oral request, a copy of any or all documents referred to above which have been or may be incorporated by reference into this prospectus but not delivered with this prospectus, excluding exhibits to those documents unless they are specifically incorporated by reference into those documents. You may request a copy of these documents by writing or telephoning us at the following address.

Krystal Biotech, Inc.
2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(412) 586-5830
Attention: J. Christopher Naftzger, Esq.
Chief Legal Officer and Corporate Secretary

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and any accompanying prospectus supplement, as well as the documents incorporated by reference therein, contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and releases issued by the SEC and within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Exchange Act. Forward-looking statements include, among others, information concerning our strategy, future operations, future financial position, future revenue, projected expenses, business prospects, and plans and objectives of management. 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 contained in this prospectus include, but are not limited to, statements about the following:

- the initiation, timing, progress and results of preclinical and clinical trials for B-VEC, KB105 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 that the COVID-19 pandemic and measures to prevent its spread may have on our business operations, access to capital, research and development activities, and preclinical and clinical trials for B-VEC, KB105 and any other product candidates;
- the timing, scope or results of regulatory filings and approvals, including timing of final US Food and Drug Administration marketing and other regulatory approval of B-VEC and KB105;
- our ability to achieve certain accelerated or orphan drug designations from the FDA;
- our estimates regarding the potential market opportunity for B-VEC, KB105 and any other product candidates;
- our research and development programs for our product candidates;
- our plans and ability to successfully develop and commercialize our product candidates, including B-VEC, KB105 and our other 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 or obtain additional funding;

- our estimates regarding expenses, future revenue, 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;
- any statements regarding compliance with the listing standards of The NASDAQ Capital Market;
- 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” and elsewhere in this prospectus. 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 prospectus 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 prospectus. You should read this prospectus and the documents that we have filed as exhibits to the registration statement, of which this prospectus is a part, 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.

PROSPECTUS SUMMARY

The following summary highlights selected information contained elsewhere or incorporated by reference in this prospectus. This summary does not contain all of the information you should consider before investing in the securities. Before making an investment decision, you should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading "Risk Factors" in this prospectus, the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

In this prospectus, unless we indicate otherwise or the context requires, references to the "Company," "Krystal," "we," "our," "ours," and "us" refer to Krystal Biotech, Inc. and its consolidated subsidiary. The following summary is qualified in its entirety by the more detailed information and financial statements and notes thereto included elsewhere in this prospectus.

Krystal Biotech, Inc.

Krystal Biotech, Inc. (the "Company," "Krystal," "we," or "us," or other similar pronouns) is a clinical-stage gene therapy company dedicated to developing and commercializing novel medicines for patients suffering from skin diseases. We have developed a proprietary gene therapy platform to develop off-the-shelf treatments for skin diseases for which we believe there are no known effective treatments. Our platform consists of a patented engineered viral vector based on the herpes simplex virus type 1, or HSV-1, containing skin-optimized gene transfer technology, which we refer to as the Skin TARgeted Delivery, or STAR-D, platform. We are initially using our STAR-D platform to develop treatments for rare or orphan monogenic dermatological indications caused by the absence of or a mutation in a single gene. We plan to leverage our platform in the future to expand our pipeline to include non-monogenic dermatological indications and skin conditions.

Beremagene Geperpavec ("B-VEC")

Our lead product candidate, B-VEC, seeks to use topical gene therapy to treat dystrophic epidermolysis bullosa, or DEB, a rare and severe monogenic skin disease for which there is currently no approved treatment. 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, or COL7, that forms anchoring fibrils that bind the dermis, or inner layer of the skin, to the epidermis, or 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.

In October 2019, we announced positive results from our Phase 1/2 clinical trial of B-VEC at Stanford University. The Phase 1 portion of the trial commenced 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 in June 2019. We anticipate commencing pivotal Phase 3 FDA trials in the first half of 2020.

The U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or 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, in 2019, the FDA granted Regenerative Medicine Advanced Therapy, or RMAT, to B-VEC for the treatment of DEB and the EMA granted PRIority MEdicines, or PRIME, eligibility for B-VEC to treat DEB. The PRIME designation is awarded by the EMA to promising medicines that target an unmet medical need.

KB105

Our second pipeline candidate, KB105, delivers functional human transglutaminase-1, or TGM1 genes using our gene therapy platform to patients with TGM1-deficient autosomal recessive congenital ichthyosis, or ARCI. 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 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 and trans-epidermal exposure to unwanted toxins and surface microorganisms, greatly increasing the risk of infection and sepsis. Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life. There are currently no treatments targeting molecular correction of this disease.

In September 2019, we initiated a Phase 1/2 clinical trial of KB105. We anticipate interim Phase 1/2 clinical readouts in the first half of 2020.

The FDA and EMA have each granted B-VEC orphan drug designation for the treatment of DEB, and the FDA has granted KB105 fast track designation and rare pediatric designation for the treatment of DEB. We received the designation of “rare pediatric disease” for KB105 in August 2018 which makes B-VEC eligible to apply for a Rare Pediatric Priority Review Voucher.

KB301

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. The goal of skin biorejuvenation is, in part, to enhance the synthesis of human dermal collagens (*i.e.*, neocollagenesis), thereby correcting the molecular defect underlying the aged phenotype. We believe that our approach of directed expression of full-length human type 3 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 and other superficial skin defects.

We anticipate filing an Investigational New Drug, or IND, application in the second half of 2020.

KB104

KB104 is designed to deliver functional Serine Protease Inhibitor Kazal-type 5, or SPINK5, genes using our gene therapy platform to patients suffering from Netherton Syndrome, which is a debilitating monogenic autosomal recessive skin disorder that causes defective keratinization, severe skin barrier defects, and recurrent infections. Infants with severe Netherton Syndrome symptoms are 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.

KB407

We are developing KB407 as a non-invasive inhaled gene therapy product for the treatment of cystic fibrosis, or CF, and are currently in the pre-clinical phase with plans to file an IND for KB407 in 2021.

CF, the most common inherited genetic disorder in the United States, is caused by mutations in the gene encoding cystic fibrosis transmembrane conductance regulator, or CFTR. Lack of functional CFTR 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 US Cystic Fibrosis Foundation, or 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 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.

Patents

In January 2020, Krystal diversified its patent estate through the issuance of US Patent and Trademark Office, or USPTO, USPTO”) patent number 10,525,090 covering our second product candidate, KB105, as well as medical applications of this product for treating ARCI. We believe the speed in which the patent prosecution was successfully concluded for this application is indicative of Krystal’s pioneering work in HSV-based gene therapies in the field of dermatology.

In December 2019, Krystal strengthened its international patent portfolio covering our lead product candidate, B-VEC, when the European Patent Office issued an intent to grant European patent application number 16826873 directed, in part, to pharmaceutical compositions comprising B-VEC, as well as uses thereof.

In October 2019, the USPTO granted the Company US patent number 10,441,614 covering its fully integrated vector platform, STAR-D, for skin-targeted therapeutics, as well as methods of its use for delivering any effector of interest to the skin. This new patent provides further validation of the Company’s novel work in the field of skin diseases leveraging its HSV-1-based gene therapy technologies.

In September 2019, the Australian patent office granted the Company its first foreign patent (Application No. 2016401692) in Australia for its lead product candidate B-VEC. This patent covers pharmaceutical compositions comprising B-VEC, as well as medical uses such as the treatment of wounds, disorders, or diseases of the skin, particularly those found in epidermolysis bullosa patients.

On December 18, 2018, the USPTO granted US Patent No. 10,155,016 which covers compositions containing B-VEC, formulated for alternate routes of administration.

On January 16, 2018, we announced that the USPTO had granted US Patent No. 9,877,990, which covers compositions comprising HSV vectors encoding certain effectors and methods of using the same for providing prophylactic, palliative or therapeutic relief of a wound, disorder or disease of the skin. A corresponding international patent application has been filed in accordance with the Paris Cooperation Treaty, which has entered into the national phase in more than ten foreign jurisdictions.

We believe that the granting of these patents, which are entirely owned by the Company, protects our core STAR-D viral platform 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 IP 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.

Other

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. On June 19, 2018, we incorporated Krystal Australia Pty Ltd, an Australian proprietary limited company, for the purposes of undertaking preclinical and clinical studies in Australia. On April 24, 2019, we incorporated Jeune, Inc. in Delaware, a wholly-owned subsidiary, for the purposes of undertaking preclinical studies for aesthetic skin conditions. To date, our operations have been focused on organizing and staffing our company, developing our proprietary platform, identifying potential product candidates, undertaking preclinical studies and clinical trials, and developing an in-house cGMP facility.

In December 2019, a new strain of coronavirus, or COVID-19, was first reported in Wuhan, China. In March 2020, the World Health Organization declared COVID-19 a pandemic and certain governments, including the Commonwealth of Pennsylvania where the Company's primary offices, laboratory and manufacturing spaces are located, enacted stay-at-home orders, and sweeping restrictions to travel were initiated by corporations and governments. To protect the health of its employees, and their families and communities, the Company has restricted access to its offices to personnel who must perform critical activities that must be completed on-site, limited the number of such personnel that can be present at our facilities at any one time, and requested that many of our employees work remotely. The extent of COVID-19's effect on the Company's clinical, operational and financial performance will depend on future developments, including the duration, spread and intensity of the pandemic, and additional protective measures implemented by the governmental authorities or the Company to protect its employees, all of which are uncertain and difficult to predict considering the rapidly evolving landscape. As a result, it is not currently possible to ascertain the overall impact of COVID-19 on the Company's business. However, if the pandemic continues to evolve into a severe

worldwide health crisis, the disease could have a material adverse effect on the Company's business, results of operations, financial condition, and cash flows.

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 or KB105, planned preclinical studies for our other product candidates, or our operations. Our funds may not be sufficient to enable us to seek marketing approval to commercially launch B-VEC or KB105. Accordingly, to obtain marketing approval for and to commercialize any of our product candidates, we may be required to obtain further funding through public or private equity offerings, debt financings, collaboration and licensing arrangements. 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.

Description of Securities

We may offer shares of our common stock or preferred stock, various series of debt securities, warrants or other rights to purchase common stock or preferred stock, or units consisting of combinations of the foregoing, either individually or in combination with other securities, in each case from time to time under this prospectus, together with the applicable prospectus supplement or any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. At the time we offer a type or series of securities, we will provide a prospectus supplement describing the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- voting or other rights;
- rates and times of payment of interest, dividends or other payments;
- original issue discount;
- maturity;
- ranking;
- restrictive covenants;
- redemption, conversion, exercise, exchange, settlement or sinking fund terms, including prices or rates, and any provisions for changes to or adjustments in such prices or rates and in the securities or other property receivable upon conversion, exercise, exchange or settlement;
- any securities exchange or market listing arrangements; and
- important U.S. federal income tax considerations.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents incorporated by reference in this prospectus.

We may sell the securities directly to investors or to or through underwriters, dealers or agents. We and our underwriters, dealers or agents reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through underwriters or agents, we will include in the applicable prospectus supplement (a) the names of the underwriters or agents and applicable fees, discounts and commissions to be paid to them, (b) details regarding over-allotment options, if any, and (c) net proceeds to us, if any.

Common Stock. We may issue shares of our common stock from time to time. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders. 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. 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. Our common stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions. In this prospectus, we have summarized certain general features of the common stock under the heading "Description of Capital Stock—Common Stock." We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Preferred Stock. We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders.

If we sell any series of preferred stock under this prospectus, we will fix the designations, voting powers, preferences and rights of the preferred stock of each series we issue under this prospectus, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that contains the terms of the series of preferred stock we are offering. In this prospectus, we have summarized certain general features of the preferred stock under "Description of Capital Stock—Preferred Stock." We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities. We may issue debt securities from time to time, in one or more series, as senior, subordinated or junior subordinated, convertible or non-convertible and secured or unsecured debt. Any senior debt securities will rank equally with any unsubordinated debt. Subordinated debt securities will rank equally with any other subordinated debt of the same ranking we may issue. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities at predetermined conversion rates, and conversion may be mandatory or at the holder's option.

Debt securities will be issued under one or more indentures-contracts between us and a national banking association or other eligible party acting as trustee. In this prospectus, we have summarized certain general features of the debt securities under the heading "Description of Debt Securities." You should read the prospectus supplements, any free writing prospectus we may authorize and the indentures, supplemental indentures and forms of debt securities relating to any series of debt securities we may offer. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Warrants, Other Rights and Units. We may, from time to time issue warrants or other rights (together, "Rights"), in one or more series, for the purchase of common stock or preferred stock. We may issue such Rights independently or together with such securities, and such Rights may be attached to or separate from them. We may issue securities in units, or Units, each consisting of two or more types of securities. For example, we might issue Units consisting of a combination of common stock and warrants to purchase common stock. In this prospectus, we have summarized certain general features of the Rights and Units under the heading "Description of Warrants, Other Rights and Units." We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to the particular series of Rights and/or Units being offered, as well as the form of Rights and/or Rights agreement and Rights certificate, as applicable, that contain the terms of the warrants. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of Rights and/or Rights agreement and Rights certificate, as applicable, that contain the terms of the particular series of Rights we are offering, and any supplemental agreements, before the issuance of such Rights.

Rights may be issued under a Rights agreement that we enter into with a Rights agent. We will indicate the name and address of the Rights agent, if any, in the applicable prospectus supplement relating to a particular series of Rights.

NASDAQ Capital Market Listing

Our common stock is listed on The NASDAQ Capital Market under the symbol "KRYS." The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on The NASDAQ Capital Market or any other securities market or other exchange of the securities covered by the applicable prospectus supplement.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of relief from certain reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- reduced obligations with respect to financial data, including presenting only two years of audited financial statements;
- an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act;
- reduced disclosure about our executive compensation arrangements in our periodic reports, proxy statements and registration statements; and
- exemptions from the requirements of holding non-binding advisory votes on executive compensation or golden parachute arrangements.

We may take advantage of these provisions for up to five years or such earlier time that we no longer qualify as an emerging growth company. We would cease to be an emerging growth company if we have more than $1.07 billion in total annual gross revenues, qualify as a "large accelerated filer" as defined under the Exchange Act or issue more than $1.0 billion of non-convertible debt over a three-year period. We may choose to take advantage of some but not all of these reduced reporting burdens. For example, we intend to take advantage of the reduced reporting requirements with respect to disclosure regarding our executive compensation arrangements, have presented only two years of audited financial statements and only two years of related "Management's Discussion and Analysis of

Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019, and have taken advantage of the exemption from auditor attestation on the effectiveness of our internal controls over financial reporting. To the extent that we take advantage of these reduced reporting burdens, the information that we provide stockholders may be different than you might obtain from other public companies in which you hold equity interests.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

RISK FACTORS

Investment in any securities offered pursuant to this prospectus involves substantial risks. Before acquiring securities from us, you should carefully consider the risk factors incorporated by reference to our most recent Annual Report on Form 10-K, our subsequent Quarterly Reports on Form 10-Q and the other information contained in this prospectus, as updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in any accompanying prospectus supplement. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities. Please also refer to the section entitled "Special Note Regarding Forward-Looking Statements" in this prospectus."

USE OF PROCEEDS

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered by us hereunder, if any, for working capital and general corporate purposes, including research and development expenses and capital expenditures.

The amounts and timing of our use of the net proceeds from this offering will depend on a number of factors, such as our funding requirements and the availability and cost of other funds at the time of sale, the timing and progress of our research and development efforts, the timing and progress of any partnering and commercialization efforts, technological advances and the competitive environment for our products. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from the sale of the securities offered by us hereunder. Accordingly, our management will have broad discretion in the timing and application of these proceeds. Pending application of the net proceeds as described above, we intend to temporarily invest the proceeds in short-term, interest-bearing instruments or other investment-grade securities, certificates of deposits or short-term U.S. government securities.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

GENERAL DESCRIPTION OF SECURITIES

We may offer shares of our common stock or preferred stock, various series of debt securities, warrants or other rights to purchase common stock or preferred stock, or units consisting of combinations of the foregoing, either individually or in combination with other securities, in each case from time to time under this prospectus, together with the applicable prospectus supplement or any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of offering. This prospectus provides you with a general description of the securities we may offer. At the time we offer a type or series of securities, we will provide a prospectus supplement describing

the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- voting or other rights;
- rates and times of payment of interest, dividends or other payments;
- original issue discount;
- maturity;
- ranking;
- restrictive covenants;
- redemption, conversion, exercise, exchange, settlement or sinking fund terms, including prices or rates, and any provisions for changes to or adjustments in such prices or rates and in the securities or other property receivable upon conversion, exercise, exchange or settlement;
- any securities exchange or market listing arrangements; and
- important U.S. federal income tax considerations.

This prospectus may not be used to offer or sell securities unless accompanied by a prospectus supplement. The prospectus supplement may add, update or change any of the information contained in this prospectus or in the documents incorporated by reference in this prospectus. We urge you to read the prospectus supplement related to any securities being offered.

We may sell the securities directly to investors or to or through underwriters, dealers or agents. We and our underwriters, dealers or agents reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through underwriters or agents, we will include in the applicable prospectus supplement (a) the names of the underwriters or agents and applicable fees, discounts and commissions to be paid to them, (b) details regarding over-allotment options, if any, and (c) net proceeds to us, if any.

The following descriptions are not complete and may not contain all the information you should consider before investing in any securities we may offer hereunder; they are summarized from, and qualified by reference to, our Certificate of Incorporation, Bylaws and the other documents referred to in the descriptions, all of which are or will be publicly filed with the SEC, as applicable. See “Where You Can Find More Information.”

DESCRIPTION OF CAPITAL 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. As of April 30, 2020, there were 17,385,809 shares of our common stock outstanding and no shares of preferred stock outstanding.

The following description summarizes the most important terms of our capital 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, or Certificate of Incorporation, and our amended and restated bylaws, or 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. See “Dividend Policy” above.

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.

Preferred Stock

Pursuant to our Certificate of Incorporation, our board of directors is authorized, subject to limitations prescribed by Delaware law, to issue from time to time up to 20,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each series and to fix the designation, powers, preferences and rights of the shares of each series and any of their qualifications, limitations or restrictions, in each case without further vote or action by our stockholders. Our board of directors may increase or decrease the number of shares of any series of preferred stock, but not below the number of shares of that series then outstanding, without any further vote or action by our stockholders. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock. We have no current plan to issue any shares of preferred stock.

The General Corporation Law of the State of Delaware, or DGCL, the state of our incorporation, provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

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 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 250 Royall Street Canton, Massachusetts 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."

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as senior, subordinated or junior subordinated, convertible or non-convertible and secured or unsecured debt. Any senior debt securities will rank equally with any unsubordinated debt. Subordinated debt securities will rank equally with any other subordinated debt of the same ranking we may issue. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities at predetermined conversion rates, and conversion may be mandatory or at the holder's option.

Debt securities will be issued under one or more indentures-contracts between us and a national banking association or other eligible party acting as trustee. Following is a summary of certain general features of debt securities we may issue; we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement, which may differ from the terms we describe below. You should read the prospectus supplements, any free writing prospectus we may authorize and the indentures, supplemental indentures and forms of debt securities relating to any series of debt securities we may offer.

General

Except as we may otherwise provide in a prospectus supplement, the relevant indenture will provide that debt securities may be issued from time to time in one or more series. The indenture will not limit the amount of debt securities that may be issued thereunder and will provide that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution, an officers' certificate or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to any series of debt securities:

- the title or designation;
- whether they will be secured or unsecured, and the terms of any security;
- whether the debt securities will be subject to subordination, and any terms thereof;
- any limit upon the aggregate principal amount;
- the date or dates on which the debt securities may be issued and on which we will pay the principal;
- the interest rate, which may be fixed or variable, or the method for determining the rate, the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining them;
- the manner in which the amounts of payment of principal of, premium or interest on the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;
- the currency of denomination;
- if payments of principal of, premium or interest will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;
- the place or places where the principal of, premium, and interest will be payable, where debt securities of any series may be presented for registration of transfer, exchange or conversion, and where notices and demands to or upon the Company in respect of the debt securities may be made;
- the form of consideration in which principal of, premium or interest will be paid;

- the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund, amortization or analogous provisions or at the option of a holder;
- the dates on which and the price or prices at which we will repurchase the debt securities at the option of holders and other detailed terms and provisions of these obligations;
- the denominations in which the debt securities will be issued, if other than denominations of $1,000 and any integral multiple thereof;
- the portion of principal amount payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- whether the debt securities are to be issued at any original issuance discount and the amount of discount with which they may be issued;
- whether the debt securities will be issued in certificated or global form and, in such case, the depositary and the terms and conditions, if any, upon which interests in such global security or securities may be exchanged in whole or in part for the individual securities represented thereby;
- provisions, if any, for defeasance in whole or in part and any addition or change to provisions related to satisfaction and discharge;
- the form of the debt securities;
- the terms and conditions upon which convertible debt securities will be convertible or exchangeable into securities or property of the Company or another person, if at all, and any additions or changes, if any, to permit or facilitate the same;
- provisions, if any, granting special rights to holders upon the occurrence of specified events;
- any restriction or condition on transferability;
- any addition or change in the provisions related to compensation and reimbursement of the trustee;
- any addition to or change in the events of default described in this prospectus or in the indenture and any change in the acceleration provisions so described;
- whether the debt securities will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;
- whether we will be restricted from incurring any additional indebtedness;
- any addition to or change in the covenants described in this prospectus or in the indenture, including terms of any restrictive covenants; and
- any other terms which may modify or delete any provision of the indenture.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the U.S. federal income tax considerations and other special considerations applicable to any debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

Except as we may otherwise provide in a prospectus supplement, the indenture will provide that we may not merge or consolidate with or into another entity, or sell other than for cash or lease all or substantially all our assets to another entity, or purchase all or substantially all the assets of another entity unless we are the surviving entity or, if we are not the surviving entity, the successor, transferee or lessee entity expressly assumes all of our obligations under the indenture or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders additional protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect them.

Events of Default under the Indenture

Except as we may otherwise provide in a prospectus supplement, the following will be events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;
- if we fail to pay the principal, or premium, if any, when due whether by maturity or called for redemption;
- if we fail to pay a sinking fund installment, if any, when due and our failure continues for 30 days;
- if we fail to observe or perform any other covenant relating to the debt securities, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to the Company.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) will necessarily constitute an event of default with respect to any other series. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

Except as we may otherwise provide in a prospectus supplement, if an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities are discount securities, that portion of the principal amount as may be specified in the terms of such securities) of and premium and accrued and unpaid interest, if any, on all such debt securities. Before a judgment or decree for payment of the money due has been obtained with respect to any series, the holders of a majority in principal amount of that series (or, at a meeting of holders at which a quorum is present, the holders of a majority in principal amount represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such

acceleration) and the Company has deposited with the indenture trustee or paying agent a sum sufficient to pay all amounts owed to the indenture trustee under the indenture, all arrears of interest, if any, and the principal and premium, if any, on the debt securities that have become due other than by such acceleration. We refer you to the relevant prospectus supplement relating to any discount securities for the particular provisions relating to acceleration of a portion of the principal amount thereof upon the occurrence of an event of default.

Subject to the terms of the indenture, and except as we may otherwise provide in a prospectus supplement, if an event of default under the indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the debenture trustee, or exercising any trust or power conferred on the debenture trustee, with respect to that series, provided that, subject to the terms of the indenture, the debenture trustee need not take any action that it believes, upon the advice of counsel, might involve it in personal liability or might be unduly prejudicial to holders not involved in the proceeding.

Except as we may otherwise provide in a prospectus supplement, a holder of the debt securities of any series will only have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies if:

- the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;
- the holders of at least a majority in aggregate principal amount outstanding of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and
- the debenture trustee does not institute the proceeding and does not receive from the holders of a majority in aggregate principal amount outstanding of that series (or at a meeting of holders at which a quorum is present, the holders of a majority in principal amount of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

Except as we may otherwise provide in a prospectus supplement, these limitations will not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, them.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

Except as we may otherwise provide in a prospectus supplement, the debenture trustee and the Company may, without the consent of any holders, execute a supplemental indenture to change the applicable indenture with respect to specific matters, including, among other things:

- to surrender any right or power conferred upon the Company;
- to provide, change or eliminate any restrictions on payment of principal of or premium, if any; provided that any such action shall not adversely affect the interests of the holders of debt securities of any series in any material respect;
- to change or eliminate any of the provisions of the indenture; provided that any such change or elimination shall become effective only when there is no outstanding debt security created prior

to the execution of such supplemental indenture that is entitled to the benefit of such provision and as to which such supplemental indenture would apply;

- to evidence the succession of another entity to the Company;
- to evidence and provide for the acceptance of appointment by a successor trustee with respect to one or more series of debt securities and to add or change provisions of the indenture to facilitate the administration of the trusts thereunder by more than one trustee;
- to cure any ambiguity, mistake, manifest error, omission, defect or inconsistency in the indenture or to conform the text of any provision in the indenture or in any supplemental indenture to any description thereof in the applicable section of a prospectus, prospectus supplement or other offering document that was intended to be a verbatim recitation of a provision of the indenture or of any supplemental indenture;
- to add to or change or eliminate any provision of the indenture as shall be necessary or desirable in accordance with any amendments to the U.S. Trust Indenture Act of 1939;
- to make any change in any series of debt securities that does not adversely affect in any material respect the interests of the holders thereof; and
- to supplement any of the provisions of the indenture to such extent as shall be necessary to permit or facilitate the defeasance and discharge of any series of debt securities; provided that any such action shall not adversely affect the interests of holders of any debt securities.

In addition, and except as we may otherwise provide in a prospectus supplement, under the indenture the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount outstanding (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount represented at such meeting) that is affected. The debenture trustee and the Company may, however, make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon redemption;
- reducing the principal amount of discount securities payable upon acceleration of maturity;
- making the principal of or premium or interest payable in currency other than that stated;
- impairing the right to institute suit for the enforcement of any payment on or after the fixed maturity date;
- materially adversely affecting the economic terms of any right to convert or exchange; and
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver; or modifying, without the written consent of the trustee, the rights, duties or immunities of the trustee.

Except for certain specified provisions, and except as we may otherwise provide in a prospectus supplement, the holders of at least a majority in principal amount of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount represented at such meeting) may, on behalf of the holders of all debt securities of that series, waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may, on behalf of all such holders, waive any past default under the indenture with respect to that series and its consequences, other than a default in the payment of the principal of, premium or any interest; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

Discharge

Except as we may otherwise provide in a prospectus supplement, the indenture will provide that we can elect to be discharged from our obligations with respect to one or more series of debt securities. In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, the premium, if any, and interest on, the debt securities of the affected series on the dates payments are due.

Form, Exchange and Transfer

Except as we may otherwise provide in a prospectus supplement, we will issue debt securities only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. Except as we may otherwise provide in a prospectus supplement, the indenture will provide that we may issue debt securities in temporary or permanent global form and as book-entry securities that will be deposited with a depositary named by us and identified in a prospectus supplement with respect to that series.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder will be able to exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities or the indenture, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

Except as we may otherwise provide in a prospectus supplement, if we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Debenture Trustee

The debenture trustee, other than during the occurrence and continuance of an event of default under the indenture, will undertake to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default, the debenture trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee will be under no obligation to exercise any of the powers given it by the indenture at the request of any holder unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of interest on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

Unless we otherwise indicate in the applicable prospectus supplement, we will pay principal of and any premium and interest at the office of the indenture trustee or, at the option of the Company, by check payable to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the debenture trustee as our sole paying agent for payments. We will name in the applicable prospectus supplement any other paying agents that we initially designate. We will maintain a paying agent in each place of payment.

All money we pay to a paying agent or the debenture trustee for the payment of principal or any premium or interest which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed and construed in accordance with the laws of the State of New York.

No Personal Liability of Directors, Officers, Employees and Stockholders

No incorporator, stockholder, employee, agent, officer, director or subsidiary of ours will have any liability for any obligations of ours or, due to the creation of any indebtedness under the debt securities, the indentures or supplemental indentures. The indentures provide that all such liability is expressly waived and released as a condition of, and as consideration for, the execution of such indentures and the issuance of the debt securities.

DESCRIPTION OF WARRANTS, OTHER RIGHTS AND UNITS

We may, from time to time, issue warrants or other rights (together, “Rights”), in one or more series, for the purchase of common stock or preferred stock. We may issue Rights independently or together with such securities, and such Rights may be attached to or separate from them. Rights will be evidenced by a Rights certificate issued under one or more Rights agreements between us and a Rights agent which will act solely as our agent in connection with the Rights and will not have any obligation or relationship of agency or trust for or with any holders or beneficial owners of Rights. We may issue securities in units, or Units, each consisting of two or more types of securities. For example, we might issue Units consisting of a combination of common stock and warrants to purchase common stock. If we issue Units, the prospectus supplement relating to the Units will contain the information described above with regard to each of the securities that is a component of the Units. In addition, the prospectus supplement relating to the Units will describe the terms of any Units we issue. The forms of any such certificates and agreements will be filed as exhibits to the registration statement of which this prospectus is a part by amendment thereof or as exhibits to a Current Report on Form 8-K incorporated herein by reference, and the accompanying prospectus supplement and such forms may add, update or change the terms and conditions of the Rights or Units described in this prospectus.

The following description of material terms and provisions of Rights and Units will generally apply to the Rights and/or Units offered by this prospectus unless we provide otherwise in the applicable prospectus supplement, which may specify different or additional terms. The following summaries are subject to, and qualified in their entirety by reference to, all the provisions of the form of Rights and/or the Rights agreement and Rights certificate, as applicable, and any supplemental agreements applicable to a particular series of Rights and/or Units that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of Rights or Units that we may offer under this prospectus, as well as any related free writing prospectus, and the complete form of Rights and/or the Rights agreement and Right certificates, as applicable, and any supplemental agreements, that contain the terms of the Rights.

The particular terms of each issue of Rights or Units will be described in the applicable prospectus supplement, including, as applicable:

- the title of the Rights or Units;
- any initial offering price;
- the title, aggregate principal amount or number and terms of the securities purchasable upon exercise of the Rights;
- the principal amount or number of securities purchasable upon exercise of each Right and the price at which that principal amount or number may be purchased upon exercise of each Right;
- the currency or currency units in which any offering price and any exercise price are payable;
- the title and terms of any related securities with which the Rights are issued and the number of the Rights issued with each security;
- any date on and after which the Rights or Units and the related securities will be separately transferable;
- any minimum or maximum number of Rights that may be exercised at any one time;
- the date on which the right to exercise the Rights will commence and the date on which the right will expire;
- a discussion of U.S. federal income tax, accounting or other considerations applicable to the Rights or Units;
- whether the Rights represented by the Rights certificates, if applicable, will be issued in registered or bearer form and, if registered, where they may be transferred and registered;

- any anti-dilution provisions of the Rights or Units;
- any redemption or call provisions applicable to the Rights;
- any provisions for changes to or adjustments in the exercise price of any Rights; and
- any additional terms of the Rights or Units, including terms, procedures and limitations relating to exchange and exercise of the Rights or Units.

Rights certificates will be exchangeable for new Rights certificates of different denominations and, if in registered form, may be presented for registration of transfer, and Rights may be exercised, at the corporate trust office of the Rights agent or any other office indicated in the related prospectus supplement. Before the exercise of Rights, holders of Rights will not be entitled to payments of any dividends, principal, premium or interest on securities purchasable upon exercise of the Rights, to vote, consent or receive any notice as a holder of and in respect of any such securities or to enforce any covenants in any indenture, or to exercise any other rights whatsoever as a holder of securities purchasable upon exercise of the Rights.

PLAN OF DISTRIBUTION

Our Plan of Distribution

We may sell the securities, from time to time, to or through underwriters or dealers, through agents or remarketing firms, or directly to one or more purchasers pursuant to:

- underwritten public offerings;
- negotiated transactions;
- block trades;
- "At the Market Offerings," within the meaning of Rule 415(a)(4) of the Securities Act, into an existing trading market, at prevailing market prices; or
- through a combination of these methods.

We may sell the securities to or through one or more underwriters or dealers (acting as principal or agent), through agents, or directly to one or more purchasers.

We may distribute securities from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

- the name or names of the underwriters, dealers or agents, if any;
- if the securities are to be offered through the selling efforts of brokers or dealers, the plan of distribution and the terms of any agreement, arrangement, or understanding entered into with broker(s) or dealer(s) prior to the effective date of the registration statement, and, if known, the identity of any broker(s) or dealer(s) who will participate in the offering and the amount to be offered through each;
- the purchase price of the securities or other consideration therefor, and the proceeds, if any, we will receive from the sale;
- if any of the securities being registered are to be offered otherwise than for cash, the general purposes of the distribution, the basis upon which the securities are to be offered, the amount of compensation and other expenses of distribution, and by whom they are to be borne;
- any delayed delivery arrangements;
- any over-allotment or other options under which underwriters may purchase additional securities from us;
- any agency fees or underwriting discounts and other items constituting agents' or underwriters' compensation;
- any public offering price;
- any discounts, commissions or commissions allowed or reallowed or paid to dealers;
- the identity and relationships of any finders, if applicable; and
- any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Unless otherwise indicated in the prospectus supplement, subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallowed or paid to dealers may change from time to time. We may use underwriters, dealers or agents with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, dealer or agent, the nature of any such relationship.

We may use a remarketing firm to offer the securities in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own account or as agents for us. These remarketing firms will offer or sell the securities pursuant to the terms of the securities. A prospectus supplement will identify any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm's compensation. Remarketing firms may be deemed to be underwriters in connection the securities they remarket.

If we offer and sell securities through a dealer, we or an underwriter will sell the securities to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale. The name of the dealer and the terms of the transaction will be set forth in the applicable prospectus supplement.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions payable to the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, the agent will act on a best-efforts basis for the period of its appointment.

Dealers and agents participating in the distribution of the securities may be deemed to be underwriters, and compensation received by them on resale of the securities may be deemed to be underwriting discounts. If such dealers or agents were deemed to be underwriters, they may be subject to statutory liabilities under the Securities Act.

We may sell securities directly to one or more purchasers without using underwriters or agents. Underwriters, dealers and agents that participate in the distribution of the securities may be underwriters as defined in the Securities Act, and any discounts or commissions they receive from us and any profit on their resale of the securities may be treated as underwriting discounts and commissions under the Securities Act.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents, underwriters and dealers with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents, underwriters or dealers may make with respect to these liabilities. Agents, underwriters and dealers, or their respective affiliates, may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters that are qualified market makers on The NASDAQ Capital Market may engage in passive market making transactions in the common stock on The NASDAQ Capital Market in accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker’s bid, however, the passive market maker’s bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

LEGAL MATTERS

The validity of the securities being offered hereby will be passed upon by Morrison & Foerster LLP, San Francisco, California. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

Mayer Hoffman McCann P.C., an independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the years ended December 31, 2019 and 2018, as set forth in its report, which is incorporated by reference in this prospectus and the registration statement. Our financial statements are incorporated by reference in reliance on Mayer Hoffman McCann P.C.’s report, given on the authority of said firm as experts in accounting and auditing.

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$150,000,000

Krystal Biotech, Inc.

Common Stock

PROSPECTUS SUPPLEMENT

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December 31, 2020