

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549**

**FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

KRYSTAL BIOTECH, INC.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

82-1080209
(I.R.S. Employer
Identification Number)

**2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(412) 586-5830**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Krish S. Krishnan
President and Chief Executive Officer
2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(412) 586-5830**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copy to:

**John Thomas
General Counsel and Corporate Secretary
2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203
(412) 586-5830**

**John Hensley
Morrison & Foerster LLP
701 Brazos Street, Suite 1100
Austin, Texas 78701
(737) 309-0700**

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this registration statement.
If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.
If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.
If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.
If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.
If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.
If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer Accelerated filer
Non-accelerated filer Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.



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 10 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 “KRY.S.” 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 April 6, 2023

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	<u>1</u>
<u>WHERE YOU CAN FIND ADDITIONAL INFORMATION</u>	<u>2</u>
<u>INFORMATION INCORPORATED BY REFERENCE</u>	<u>3</u>
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	<u>5</u>
<u>PROSPECTUS SUMMARY</u>	<u>7</u>
<u>RISK FACTORS</u>	<u>10</u>
<u>USE OF PROCEEDS</u>	<u>11</u>
<u>DIVIDEND POLICY</u>	<u>12</u>
<u>GENERAL DESCRIPTION OF SECURITIES</u>	<u>13</u>
<u>DESCRIPTION OF CAPITAL STOCK</u>	<u>14</u>
<u>DESCRIPTION OF DEBT SECURITIES</u>	<u>18</u>
<u>DESCRIPTION OF WARRANTS, OTHER RIGHTS AND UNITS</u>	<u>25</u>
<u>PLAN OF DISTRIBUTION</u>	<u>27</u>
<u>LEGAL MATTERS</u>	<u>30</u>
<u>EXPERTS</u>	<u>30</u>

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 (the “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., together with its wholly-owned subsidiaries.

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, 2022 filed with the SEC on February 27, 2023;
- our Current Report on [Form 8-K](#) filed with the SEC on March 6, 2023;
- the sections of our [Definitive Proxy Statement on Schedule 14A](#) filed with the SEC on April 4, 2023 that are incorporated by reference to our Annual Report on Form 10-K for the year ended December 31, 2022; 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: John Thomas
General Counsel 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 our product candidates, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the impact of public health crises including the COVID-19 pandemic and measures to contain or prevent these outbreaks may have on our business operations, access to capital, research and development activities, and preclinical and clinical trials for our product candidates;
- the timing, scope or results of regulatory filings and approvals, including timing of final US Food and Drug Administration (“FDA”) marketing and other regulatory approval of our product candidates;
- our ability to achieve certain accelerated or orphan drug designations from the FDA;
- our estimates regarding the potential market opportunity for our product candidates;
- our research and development programs for our product candidates;
- our plans and ability to successfully develop and commercialize our product candidates;
- our ability to identify and develop new product candidates;
- our ability to identify, recruit and retain key personnel;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- the scalability and commercial viability of our proprietary manufacturing methods and processes;
- the rate and degree of market acceptance and clinical utility of our product candidates and gene therapy, in general;
- our competitive position;
- our intellectual property position and our ability to protect and enforce our intellectual property;
- our financial performance;

- developments and projections relating to our competitors and our industry;
- our ability to establish and maintain collaborations;
- our estimates regarding expenses, future 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;
- the impact of laws and regulations; and
- any statements regarding economic conditions.

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., together with 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.

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

Our product candidates include Beremagene Geperpavec (“B-VEC”), a redosable, off-the-shelf gene therapy designed to deliver two copies of the COL7A1 gene when applied topically, directly onto an open wound; KB 104, a redosable off-the-shelf gene therapy designed to deliver two copies of the Serine Protease Inhibitor Kazal-type 5 gene to relevant skin cells when applied topically, for the treatment of Netherton Syndrome; KB105, a redosable, off the-shelf gene therapy designed to deliver two copies of the functional human transglutaminase-1 gene (“TGM1”) when applied topically, directly to a patient’s exfoliated skin, for the treatment of TGM1-deficient autosomal recessive congenital ichthyosis; KB301, an intradermal application of the gene that encodes for type III collagen, for the treatment of aesthetic skin conditions; KB407, a redosable off the-shelf gene therapy designed to deliver two copies of the full-length cystic fibrosis transmembrane conductance regulator transgene directly to the airway epithelia via inhaled (nebulized) administration, for the treatment of cystic fibrosis; and KB408, an inhaled (nebulized) formulation of our proprietary vector, designed to deliver two copies of the SERPINA1 transgene that encodes functional, full-length human protein, for the treatment of Alpha-1 antitrypsin deficiency.

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 ("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 ("Nasdaq") under the symbol "KRY5." The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on Nasdaq or any other securities market or other exchange of the securities covered by the applicable prospectus supplement.

Corporate Information

We commenced operations in April 2016. In March 2017, we converted from a California limited liability company to a Delaware C-corporation, and changed our name from Krystal Biotech, LLC to Krystal Biotech, Inc. Our principal executive offices are located at 2100 Wharton Street, Suite 701, Pittsburgh, Pennsylvania 15203, and our telephone number is (412) 586-5830. 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.

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 March 22, 2023, there were 25,787,913 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 (“Certificate of Incorporation”), and our amended and restated bylaws (“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 (“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 Bylaws or remove directors without holding a meeting of our stockholders called in accordance with our restated bylaws. Further, our Certificate of Incorporation and Bylaws provide that special meetings of our stockholders may be called only by a majority of our board of directors, the chairman of our board of directors, or our Chief Executive Officer, thus prohibiting a stockholder from calling a special meeting. These provisions might delay the ability of our stockholders to force consideration of a proposal or for stockholders controlling a majority of our capital stock to take any action, including the removal of directors.
- *Advance Notice Requirements for Stockholder Proposals and Director Nominations.* Our Bylaws provides advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our Bylaws also specifies certain requirements regarding the form and content of a stockholder's notice. These provisions may preclude our stockholders from bringing matters before our annual meeting of stockholders or from making nominations for directors at our annual meeting of stockholders if the proper procedures are not followed. We expect that these provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.
- *No Cumulative Voting.* The DGCL provides that stockholders are not entitled to the right to cumulate votes in the election of directors unless a corporation's certificate of incorporation provides otherwise. Our Certificate of Incorporation does not provide for cumulative voting.
- *Directors Removed Only for Cause.* Our Certificate of Incorporation provides that stockholders may remove directors only for cause and only by the affirmative vote of the holders of at least two-thirds of our outstanding common stock.
- *Amendment of Charter Provisions.* Any amendment of the above expected provisions in our Certificate of Incorporation requires approval by holders of at least two-thirds of our outstanding common stock.
- *Issuance of Undesignated Preferred Stock.* Our board of directors has the authority, without further action by the stockholders, to issue up to 20,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock will enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or other means.
- *Choice of Forum.* Our Certificate of Incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our Certificate of Incorporation or our Bylaws; any action to interpret, apply, enforce or determine the validity of our Certificate of Incorporation or our Bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal

proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent's address is 150 Royall Street Canton, 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 Nasdaq under the symbol "KRY5."

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 indenture 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 indenture 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 indenture 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 indenture 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 indenture trustee, or exercising any trust or power conferred on the indenture trustee, with respect to that series, provided that, subject to the terms of the indenture, the indenture 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 indenture 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 indenture trustee to institute the proceeding as trustee; and
- the indenture 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 indenture 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 indenture 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 indenture 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 indenture 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 depository 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 Indenture Trustee

The indenture 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 indenture 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 indenture 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 indenture 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 indenture 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 (“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 reallocated 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 Nasdaq may engage in passive market making transactions in the common stock on Nasdaq 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. 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

The consolidated financial statements of Krystal Biotech, Inc. as of December 31, 2022 and for the year ended December 31, 2022, and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2022, have been incorporated by reference in this prospectus and the registration statement in reliance upon the reports of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

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, 2021 and 2020, 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.

You should rely only on the information contained in this prospectus. We have not authorized any dealer, broker, salesperson or any other person to provide you with information or to make any representations different from those contained in this prospectus or incorporated herein by reference. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of the shares. This prospectus does not constitute an offer or solicitation by anyone in any jurisdiction in which such offer or solicitation is not authorized or in which the person making such offer is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.



Krystal Biotech, Inc.

**Common Stock
Preferred Stock
Debt Securities
Warrants
Rights Units**

PROSPECTUS

April 6, 2023

PART II

INFORMATION NOT REQUIRED IN THE PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

The following table sets forth an estimate of the fees and expenses, other than the underwriting discounts and commissions, payable by us in connection with the issuance and distribution of the securities being registered. All the amounts shown are estimates.

SEC registration fee	*
FINRA fee	**
NASDAQ listing fee	**
Accounting fees and expenses	**
Legal fees and expenses	**
Transfer agent and registrar fees and expenses	**
Trustee fees and expenses (including counsel fees and expenses)	**
Printing and engraving expenses	**
Miscellaneous expenses	**
Total	\$ **

* Deferred in accordance with Rule 456(b) and Rule 457(r) under the Securities Act.

** Since an indeterminate amount of securities is covered by this registration statement, the expenses in connection with the issuance and distribution of the securities are not currently determinable. An estimate of the aggregate expenses in connection with the sale and distribution of securities being offered will be included in any applicable prospectus supplement.

Item 15. Indemnification of Directors and Officers.

We are incorporated under the laws of the State of Delaware. Section 102 of the Delaware General Corporation Law permits a corporation to eliminate the personal liability of directors of a corporation to the corporation or its stockholders for monetary damages for a breach of fiduciary duty as a director, except where the director breached his duty of loyalty, failed to act in good faith, engaged in intentional misconduct or knowingly violated a law, authorized the payment of a dividend or approved a stock repurchase in violation of Delaware corporate law or obtained an improper personal benefit.

Section 145 of the Delaware General Corporation Law provides that a corporation has the power to indemnify a director, officer, employee or agent of the corporation and certain other persons serving at the request of the corporation in related capacities against expenses (including attorneys' fees), judgments, fines and amounts paid in settlements actually and reasonably incurred by the person in connection with an action, suit or proceeding to which he is or is threatened to be made a party by reason of such position, if such person acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation, and, in any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful, except that, in the case of actions brought by or in the right of the corporation, no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Court of Chancery or such other court shall deem proper.

As permitted by the Delaware General Corporation Law, our second amended and restated certificate of incorporation and amended and restated bylaws provide that: (i) we are required to indemnify our directors and officers to the fullest extent permitted by the Delaware General Corporation Law; (ii) we may, in our discretion, indemnify our employees and agents as set forth in the Delaware General Corporation Law; (iii) we are required,

upon satisfaction of certain conditions, to advance all expenses incurred by our directors and officers in connection with certain legal proceedings; (iv) the rights conferred in the bylaws are not exclusive; and (v) we are authorized to enter into indemnification agreements with our directors, officers, employees and agents.

We have entered into indemnification agreements with our directors and executive officers that require us to indemnify them against expenses, judgments, fines, settlements and other amounts that any such person becomes legally obligated to pay (including with respect to a derivative action) in connection with any proceeding, whether actual or threatened, to which such person may be made a party by reason of the fact that such person is or was a director or officer of us or any of our affiliates, provided such person acted in good faith and in a manner such person reasonably believed to be in, or not opposed to, our best interests. We maintain a directors' and officers' liability insurance policy. The policy insures directors and officers against unindemnified losses arising from certain wrongful acts in their capacities as directors and officers and reimburses us for those losses for which we have lawfully indemnified the directors and officers. The policy contains various exclusions.

In addition, the form of underwriting agreement to be filed as Exhibit 1.1 to this Registration Statement provides for indemnification by the underwriters of us and our officers and directors for certain liabilities arising under the Securities Act of 1933, as amended, or otherwise.

Item 16. Exhibits

Exhibit No.	Description
1.1*	Form of Underwriting Agreement.
3.1#	Second Amended and Restated Certificate of Incorporation of Krystal Biotech, Inc. (incorporated herein by reference to Exhibit 3.1 to the Current Report on Form 8-K of Krystal Biotech, Inc. filed with the SEC on September 25, 2017).
3.2#	Amended and Restated Bylaws of Krystal Biotech, Inc. (incorporated herein by reference to Exhibit 3.2 to the Current Report on Form 8-K of Krystal Biotech, Inc. filed with the SEC on September 25, 2017).
4.1#	Form of Common Stock Certificate (incorporated herein by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1/A filed on September 14, 2017).
4.2*	Specimen Preferred Stock Certificate and Form of Certificate of Designation of Preferred Stock.
4.3*	Form of Common Stock Warrant Agreement and Warrant Certificate.
4.4*	Form of Preferred Stock Warrant Agreement and Warrant Certificate.
4.5#	Form of Indenture (including form of Debt Securities) (incorporated by reference to Exhibit 4.5 to the Registrant's Registration Statement on Form S-3 filed on May 4, 2020).
4.6*	Form of Rights Agreement (including form of Rights).
5.1†	Opinion of Morrison & Foerster LLP.
23.1†	Consent of KPMG LLP.
23.2†	Consent of Mayer Hoffman McCann P.C.
23.3†	Consent of Morrison & Foerster LLP (included in Exhibit 5.1).
24.1†	Power of Attorney (included on signature page hereto).
25.1††	Statement of Eligibility of Trustee on Form T-1.
107†	Filing Fee Table.

* To be filed, if necessary, as an exhibit to a post-effective amendment to this registration statement or as an exhibit to a Current Report on Form 8-K to be filed by the registrant in connection with a specific offering, and incorporated herein by reference.

Previously filed.

† Filed herewith.

†† To be filed pursuant to Section 305(b)(2) of the U.S. Trust Indenture Act of 1939, as amended, as applicable.

Item 17. Undertakings.

(a) The undersigned registrant hereby undertakes:

- (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:
 - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;
 - (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Filing Fee Table" filed as an exhibit to the effective registration statement; and
 - (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement.

- (2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:
 - (i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and
 - (ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no

statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

- (5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities:

The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

- (i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and
- (iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

- (b) The undersigned registrant hereby undertakes that, for the purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

- (c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

- (d) The undersigned registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Trust Indenture Act.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Pittsburgh, Commonwealth of Pennsylvania, on April 6, 2023.

KRYSTAL BIOTECH, INC.

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

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that the undersigned officers and directors of Krystal Biotech, Inc., a Delaware corporation, do hereby constitute and appoint Krish S. Krishnan as the lawful attorney-in-fact and agent with full power of substitution or re-substitution, with full power and authority to do any and all acts and things in our name and on our behalf in our capacities as officers and directors and to execute any and all instruments for us and in our names in the capacities indicated below which said attorney-in-fact and agent determines may be necessary or advisable or required to enable said corporation to comply with the Securities Act of 1933, as amended, and any rules or regulation or requirements of the Securities and Exchange Commission in connection with this registration statement. Without limiting the generality of the foregoing power and authority, the powers granted include the power and authority to sign the names of the undersigned officers and directors in the capacities indicated below to this registration statement, to any and all amendments, both pre-effective and post-effective, and supplements to this registration statement and to any and all instruments or documents filed as part of or in conjunction with this registration statement or amendments or supplements thereto, and each of the undersigned hereby ratifies and confirms all that said attorney-in-fact and agent shall do or cause to be done by virtue hereof. This power of attorney may be signed in several counterparts.

IN WITNESS WHEREOF, each of the undersigned has executed this Power of Attorney as of the date indicated.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ Krish S. Krishnan Krish S. Krishnan	President and Chief Executive Officer and Director (Principal Executive Officer)	April 6, 2023
/s/ Kathryn Romano Kathryn Romano	Chief Accounting Officer (Principal Accounting and Financial Officer)	April 6, 2023
/s/ Suma M. Krishnan Suma M. Krishnan	President, R&D and Director	April 6, 2023
/s/ Daniel S. Janney Daniel S. Janney	Director	April 6, 2023
/s/ Dino A. Rossi Dino A. Rossi	Director	April 6, 2023
/s/ Kirti Ganorkar Kirti Ganorkar	Director	April 6, 2023
/s/ Julian S. Gangolli Julian S. Gangolli	Director	April 6, 2023
/s/ Christopher Mason Christopher Mason	Director	April 6, 2023
/s/Catherine Mazzacco Catherine Mazzacco	Director	April 6, 2023
/s/ E. Rand Sutherland E. Rand Sutherland	Director	April 6, 2023

Calculation of Filing Fee Tables

Form S-3
(Form Type)

Krystal Biotech, Inc.
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered and Carry Forward Securities

Security Type	Security Class Title	Fee Calculation or Carry Forward Rule	Amount Registered(1)	Proposed Maximum Offering Price Per Unit(1)	Maximum Aggregate Offering Price(1)	Fee Rate(2)	Amount of Registration Fee(2)	Carry Forward Form Type	Carry Forward File Number	Carry Forward Initial Effective Date	Filing Fee Previously Paid in Connection with Unsold Securities to Be Carried Forward
Newly Registered Securities											
Fees to Be Paid	Equity	Common Stock, par value \$0.00001 per share	457(r)								
	Equity	Preferred Stock, par value \$0.00001 per share	457(r)								
	Debt	Debt Securities	457(r)								
	Other	Warrants(3)	457(r)								
	Other	Rights	457(r)								
	Other	Units(4)	457(r)								
Fees Previously Paid	N/A		N/A	N/A	N/A	N/A	N/A	N/A			
Carry Forward Securities											
Carry Forward Securities	N/A	N/A	N/A	N/A		N/A			N/A	N/A	N/A
		Total Offering Amounts				N/A					
		Total Fees Previously Paid				N/A					
		Total Fee Offsets				N/A					
		Net Fee Due				N/A					

- (1) An indeterminate amount of the securities of each identified class is being registered as may from time to time be offered hereunder at indeterminate prices, along with an indeterminate number of securities that may be issued upon exercise, settlement, exchange or conversion of securities offered or sold hereunder or that are represented by depositary shares. Pursuant to Rule 416 under the Securities Act of 1933, as amended (the "Securities Act"), this registration statement also covers any additional securities that may be offered or issued in connection with any stock split, stock dividend or pursuant to the anti-dilution provisions of any of the securities. Separate consideration may or may not be received for securities that are issuable upon conversion, exercise or exchange of other securities.
- (2) In accordance with Securities Act Rules 456(b) and 457(r), the registrant is deferring payment of all registration fees and will pay the registration fees subsequently in advance or on a "pay-as-you-go" basis.
- (3) The warrants covered by this registration statement may be warrants for common stock or preferred stock.
- (4) Any securities registered hereunder may be sold separately or as units with other securities registered hereunder.

April 6, 2023

Board of Directors
Krystal Biotech, Inc.
2100 Wharton Street, Suite 701
Pittsburgh, Pennsylvania 15203

Re: Registration Statement on Form S-3

Ladies and Gentlemen:

We have acted as counsel to Krystal Biotech, Inc., a Delaware corporation (the “**Company**”), in connection with the preparation and filing of its registration statement on Form S-3 (the “**Registration Statement**”), filed with the Securities and Exchange Commission (the “**Commission**”) under the Securities Act of 1933, as amended (the “**Securities Act**”), relating to the proposed issuance and sale by the Company of the following securities: (i) shares of common stock, par value \$0.00001 per share (the “**Common Stock**”); (ii) shares of preferred stock, par value \$0.00001 per share (the “**Preferred Stock**”); (iii) debt securities (the “**Debt Securities**”); (iv) warrants to purchase Common Stock or Preferred Stock (the “**Warrants**”); (v) rights to purchase Common Stock or Preferred Stock (the “**Rights**”) and (vi) units consisting of two or more of the types of securities referred to above (the “**Units**” and, together with the Common Stock, the Preferred Stock, the Debt Securities, the Warrants and the Rights, the “**Securities**”), all of which may be offered and sold from time to time on a delayed or continuous basis in accordance with Rule 415 promulgated under the Securities Act, as set forth in the prospectus which forms a part of the Registration Statement, and as to be set forth in one or more supplements to the prospectus.

As counsel for the Company, we have examined the Registration Statement and originals or copies, certified or otherwise identified to our satisfaction, of such agreements, instruments, documents, certificates and records as we have deemed relevant and necessary for the basis of our opinions hereinafter expressed. In such examination, we have assumed: (i) the authenticity of original documents and the genuineness of all signatures; (ii) the conformity to the originals of all documents submitted to us as copies; (iii) the truth, accuracy and completeness of the information, representations and warranties contained in the agreements, instruments, documents, certificates and records that we have reviewed; and (iv) the legal capacity of all natural persons. As to all matters of fact, we have relied on the representations and statements of fact made in the documents so reviewed, and we have not independently established or verified the facts so relied on. This opinion letter is given, and all statements herein are made, in the context of the foregoing.

For purposes of this opinion letter, we have assumed that: (i) the issuance, sale, amount and terms of any Securities to be offered from time to time under the Registration Statement will have been duly authorized and established by proper action (“**Board Action**”) of the Board of Directors of the Company or a duly authorized committee of such Board of Directors in accordance with the Company’s Certificate of Incorporation (as amended, the “**Charter**”) and bylaws and applicable provisions of Delaware corporate law, in a manner that does not violate any law, government or court-imposed order or restriction or agreement or instrument then binding on the Company or otherwise impair the valid or binding nature of the obligations represented by the applicable Securities; (ii) at the time of offer, issuance and sale of any Securities, the Registration Statement, and any amendments thereto (including post-effective amendments), will have been declared effective under the Securities Act, and no stop order suspending its effectiveness will have been issued and remain in effect; (iii) a prospectus supplement will have been filed with the Commission describing the Securities offered thereby; (iv) all Securities will be issued and sold in compliance with applicable U.S. federal and state securities laws and in the manner stated in the Registration Statement and the applicable prospectus supplement; (v) prior to the issuance of any

Securities, a definitive purchase, underwriting or similar agreement with respect to any Securities offered will have been duly authorized and validly executed and delivered by the Company and the other parties thereto; (vi) any Preferred Stock will be issued in one or more series and the number of shares and the designation, powers, preferences and rights of the Preferred Stock of such series and any qualifications, limitations or restrictions thereon, will be set forth in a certificate of designation (each, a “**Certificate of Designation**”); (vii) any Debt Securities will be issued under the form of indenture, to be between the Company and a bank, trust company, or other financial institution identified therein as trustee (the “**Trustee**”) filed as Exhibit 4.5 to the Registration Statement, as such indenture may be supplemented from time to time (the “**Indenture**”); (viii) any Warrants will be issued under one or more warrant agreements, each to be between the Company and a bank, trust company, or other financial institution identified therein as warrant agent (each a “**Warrant Agreement**”); (ix) any Rights will be issued under one or more rights agreements (each, a “**Rights Agreement**”) each to be entered into by the Company and a rights agent (each, a “**Rights Agent**”) (x) any Units will be issued under one or more unit agreements (each, a “**Unit Agreement**”), each to be entered into by the company and a unit agent (each, a “**Unit Agent**”); (xi) if being sold by the issuer thereof, the Securities will be delivered against payment of valid consideration therefor and in accordance with the terms of the applicable Board Action authorizing such sale and any applicable underwriting agreement or purchase agreement and as contemplated by the Registration Statement and/or the applicable prospectus supplement; (xii) the Company will remain a Delaware corporation; (xiii) upon the issuance of any shares of Common Stock, including Common Stock which may be issued upon conversion or exercise of any other Securities convertible into or exercisable for Common Stock (“**Common Securities**”), the total number of shares of Common Stock issued and outstanding will not exceed the total number of shares of Common Stock that the Company is then authorized to issue under the Charter; (xiv) upon the issuance of any Preferred Stock, including Preferred Stock which may be issued upon conversion or exercise of any other Securities convertible into or exercisable for Preferred Stock, the total number of shares of Preferred Stock issued and outstanding, and the total number of issued and outstanding shares of the applicable class or series of Preferred Stock designated pursuant to the Charter, will not exceed the total number of shares of Preferred Stock or the number of shares of such class or series of Preferred Stock that the Company is then authorized to issue under the Charter; (xv) with respect to any Preferred Stock, a Certificate of Designation relating to the Preferred Stock to be issued by the Company will be adopted by the Board of Directors and the Certificate of Designation will be filed with and accepted for record by the Delaware Secretary of State prior to their issuance; (xvi) the terms of the Securities will conform in all material respects to the respective descriptions thereof in the prospectus which is part of the Registration Statement; (xvii) certificates, if required, representing the Securities will be duly executed and delivered and, to the extent required by any applicable agreement, duly authenticated and countersigned; (xviii) the laws of the State of New York will be the governing law with respect to any Indenture, Warrant Agreement, Rights Agreement and Unit Agreement; and (xix) any Securities convertible into or exercisable, exchangeable or redeemable for any other Securities will be duly converted, exercised, exchanged or redeemed in accordance with their terms.

To the extent that the obligations of the Company with respect to the Securities may be dependent upon such matters, we assume for purposes of this opinion that, with respect to each instrument or agreement referred to in or otherwise relevant to the opinions set forth herein (each, an “**Instrument**”), that each other party to such Instrument is duly organized, validly existing and in good standing under the laws of its jurisdiction of organization, is duly qualified to engage in the activities contemplated by such Instrument; that such Instrument will have been duly authorized, executed and delivered by the other party and will constitute the legal, valid and binding obligation of the other party enforceable against the other party in accordance with its terms; that such other party will be in compliance with respect to performance of its obligations under the Instrument with all applicable laws and regulations; that such

other party will have the requisite organizational and legal power and authority to perform its obligations under the Instrument; and that a Statement of Eligibility of the Trustee on Form T-1 has been properly filed with the Commission.

Based upon, subject to and limited by the foregoing, we are of the opinion that:

1. After the Board of Directors of the Company has taken appropriate Board Action, the Common Stock will be duly authorized and, when and if issued and delivered in accordance with the Registration Statement and the applicable Board Action and consideration therefor has been received by the Company, the Common Stock will be validly issued, fully paid and nonassessable.
2. After the Board of Directors of the Company has taken appropriate Board Action, the Preferred Stock will be duly authorized and, when and if issued and delivered in accordance with the Registration Statement and the applicable Board Action and consideration therefor has been received by the Company, the Preferred Stock will be validly issued, fully paid and nonassessable.
3. After the Board of Directors of the Company has taken appropriate Board Action and upon the due execution and delivery of an Indenture on behalf of the Company and the Trustee, the Debt Securities will be duly authorized and, upon (a) due authentication by the Trustee, (b) the issuance and delivery of the Debt Securities in accordance with the Registration Statement and the applicable Board Action, and (c) receipt of the consideration therefor by the Company, the Debt Securities will constitute valid and binding obligations of the Company, enforceable in accordance with their terms.
4. After the Board of Directors of the Company has taken appropriate Board Action and upon the due execution and delivery of the Warrant Agreements by the Company and the applicable Warrant Agent and due authentication of the Warrants by such Warrant Agent, the Warrants will be duly authorized and, when and if issued and delivered in accordance with the Registration Statement and the applicable Board Action and consideration therefor has been received by the Company, the Warrants will constitute valid and binding obligations of the Company.
5. After the Board of Directors of the Company has taken appropriate Board Action and upon the due execution and delivery of the Rights Agreements, the Rights will be duly authorized and, when and if issued and delivered in accordance with the Registration Statement and the applicable Board Action and consideration therefor has been received by the Company, the Rights will constitute valid and binding obligations of the Company.
6. After the Board of Directors of the Company has taken appropriate Board Action and upon the due execution and delivery of the Unit Agreements, the Units will be duly authorized and, when and if issued and delivered in accordance with the Registration Statement and the applicable Board Action and consideration therefor has been received by the Company, the Units will constitute valid and binding obligations of the Company.

Our opinion that any document is legal, valid and binding is qualified as to:

- (a) limitations imposed by bankruptcy, insolvency, reorganization, arrangement, fraudulent conveyance, moratorium or other laws relating to or affecting the rights of creditors generally;
- (b) rights to indemnification and contribution, which may be limited by applicable law or equitable principles; and

- (c) general principles of equity, including without limitation concepts of materiality, reasonableness, good faith and fair dealing, and the possible unavailability of specific performance or injunctive relief and limitation of rights of acceleration, regardless of whether such enforceability is considered in a proceeding in equity or at law.

This opinion letter is based as to matters of law solely on (i) the Delaware General Corporation Law, as amended, and (ii) applicable provisions of the laws of the State of New York (but not including any laws, statutes, ordinances, administrative decisions, rules or regulations of any political subdivision of the State of New York). We express no opinion herein as to any other laws, statutes, ordinances, rules or regulations. As used herein, the term “Delaware General Corporation Law, as amended” includes the statutory provisions contained therein, all applicable provisions of the Delaware Constitution and reported judicial decisions interpreting these laws. Our opinion is based upon current statutes, rules, regulations, cases and official interpretive opinions, and it covers certain items that are not directly or definitively addressed by such authorities.

This opinion letter has been prepared for your use in connection with the Registration Statement. We assume no obligation to advise you of any changes in the foregoing subsequent to the effective date of the Registration Statement.

We hereby consent to the filing of this opinion letter as Exhibit 5.1 to the Registration Statement with the Commission and to reference to us under the caption “Legal Matters” in the prospectus forming a part of the Registration Statement. In giving such consent, we do not hereby admit that we are acting within the category of persons whose consent is required under Section 7 of the Securities Act or the rules or regulations of the Commission thereunder.

Sincerely,

/s/ Morrison & Foerster LLP



KPMG LLP
BNY Mellon Center
Suite 3400
500 Grant Street
Pittsburgh, PA 15219-2598

Consent of Independent Registered Public Accounting Firm

We consent to the use of our reports dated February 27, 2023, with respect to the consolidated financial statements of Krystal Biotech, Inc., and the effectiveness of internal control over financial reporting, incorporated herein by reference, and to the reference to our firm under the heading "Experts" in the prospectus.

/s/ KPMG LLP
Pittsburgh, Pennsylvania
April 6, 2023

KPMG LLP, a Delaware limited liability partnership and a member firm of the KPMG global organization of independent member firms affiliated with KPMG International Limited, a private English company limited by guarantee.

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in this Registration Statement on Form S-3 and related Prospectus dated April 6, 2023 of our report dated February 28, 2022, with respect to the consolidated financial statements of Krystal Biotech, Inc. as of December 31, 2021, and the related statements of operations and comprehensive loss, stockholders' equity and cash flows for the years ended December 31, 2021 and 2020, and to the reference to us under the heading "Experts" in this Prospectus which is part of this Registration Statement.

/s/ Mayer Hoffman McCann P.C.

San Diego, California

April 6, 2023