CUE™
BIOPHARMA

IMMUNE RESPONSES, ON CUE™

ANNUAL REPORT 2022

ABOUT CUE BIOPHARMA

Cue Biopharma, a clinical-stage biopharmaceutical company, is developing a novel class of injectable biologics to selectively engage and modulate disease-specific T cells directly within the patient's body. The company's proprietary platform, Immuno-STAT™ (*Selective Targeting and Alteration of T cells*) and biologics are designed to harness the body's intrinsic immune system as T cell engagers without the need for ex vivo manipulation or broad systemic modulation.

Headquartered in Boston, Massachusetts, we are led by an experienced management team and independent Board of Directors with deep expertise in immunology and immuno-oncology as well as the design and clinical development of protein biologics.

MANAGEMENT TEAM

Daniel Passeri, M.Sc., J.D.
Chief Executive Officer

Anish Suri, Ph.D.
President & Chief Scientific Officer

Matteo Levisetti, M.D.
Chief Medical Officer

Kerri-Ann Millar, CPA
Chief Financial Officer

Patricia Nasshorn
Chief Business Officer

Colin Sandercock, M.S.E., J.D.
Senior Vice President & General Counsel

BOARD OF DIRECTORS

Frank Morich, M.D., Ph.D.
Chairman of the Board

Daniel Passeri, M.Sc., J.D.
Chief Executive Officer

Peter Kiener, D.Phil.
Former Chief Scientific Officer at Sucampo

Fred Driscoll
Former Chief Financial Officer at Flexion Therapeutics

Tamar Howson
Former Executive Vice President, Corporate Business Development at Lexicon Pharmaceuticals, Inc.

Aaron Fletcher, Ph.D.
Managing Director of Bios Partners

For more information, visit **cuebiopharma.com** and follow us on Twitter **@CueBiopharma**

DEAR CUE BIOPHARMA SHAREHOLDERS,

2022 was an important year of corporate development accomplishments as we navigated through various challenges confronting the biotechnology sector. Our core mission continues to be focused on realizing the promise of the Immuno-STAT™ platform as a transformative therapeutic breakthrough in the treatment of cancer and autoimmune disease. Our science and technology address core challenges of developing effective immunotherapies most notably, selective modulation of disease-relevant T cells, durability of response and patient safety. By strategically directing a focused deployment of our corporate resources, we have positioned the company for further growth opportunities with the prospects of significant value creation for our shareholders.

We believe our ongoing clinical trials of CUE-101 and CUE-102, our first two clinical candidates from the interleukin 2 (IL-2)-based CUE-100 series, have achieved validation and platform de-risking. Importantly, the data from CUE-101 appears to provide us with options for potential registration trials, addressing significant unmet medical need for patients suffering from HPV+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). We also received Fast-Track designation for CUE-101 both as a monotherapy and in combination with pembrolizumab (KEYTRUDA®) which further supports its potential for registration trials. The composite CUE-101 clinical data are highly supportive of our central premise: that targeting the T cell receptor (TCR) via our Immuno-STAT platform enables selective delivery of cytokines, such as IL-2, to tumor-specific T cells. We believe this approach enables the achievement of a therapeutic index for IL-2, and other cytokines by avoiding and reducing the unwanted side effects of non-selective, indiscriminate activity. Importantly, we believe this approach is significantly differentiated from other IL-2 modalities being pursued, some of which have already failed due to the lack of selectivity for fighting cancers. As a reminder, our platform modularity allows us to also deploy numerous other modulatory co-stimulators beyond IL-2 based upon the same principle.

We continue to be highly encouraged by the data presented at the Society for Immunotherapy of Cancer (SITC) Annual Meeting in November 2022 on the first 10 patients enrolled at the recommended phase 2 dose (RP2D) of 4 mg/kg of CUE-101 in the combination trial with KEYTRUDA as a first-line treatment for HPV+ R/M HNSCC. To date, follow up analysis on these initial 10 patients, as well as the additional patients dosed and evaluated at the RP2D, continue to support what appears to be a doubling of the overall response rate (ORR) i.e., ~ 40% ORR in combination vs. ~ 20% ORR of KEYTRUDA alone, based upon the reported historical data. These observations support the premise that CUE-101, and by implication, the entire CUE-100 series, mechanistically complement immune checkpoint inhibitors (CPIs) such as KEYTRUDA. We see this as a key strategic advantage for expanding patient reach and therapeutic benefit of CPIs, which places us in a position of strength for corporate partnering. Based on the clinical data generated to date with CUE-101, we believe we are well positioned with our oncology portfolio to seek partnerships and transactions structured to ensure we

SHAREHOLDER LETTER (CONT'D)

retain involvement and optimal upside while addressing capital access for building out our promising pipeline of potentially breakthrough therapeutics.

In addition to our ongoing progress in oncology, we recently entered a strategic partnership with Ono Pharmaceuticals for the development of CUE-401, a bi-specific molecule for induction and expansion of regulatory T cells for potentially addressing a broad spectrum of autoimmune and inflammatory diseases. Importantly, this transaction provides us with requisite capital through program funding, thereby subsidizing the ongoing research and development costs, with Cue Biopharma retaining a 50% co-development option for the US market.

The accomplishments and developments of 2022 have positioned us well for what we believe will be a transformative 2023. We have the prospects for registrational paths forward for CUE-101 as a monotherapy and in combination with KEYTRUDA, and believe we are well positioned for continued advancements across our platform of assets in both oncology as well as autoimmune disease.

We would like to extend our sincere thanks and appreciation to our committed shareholders, passionate employees, board of directors, scientific advisory board, clinical investigators and our collaboration partners for their continued support, guidance and trust. Most importantly, we extend our profound appreciation and respect to the patients and their families who have participated in our clinical trials, enabling us to gain insights and knowledge essential for continued progress in the fight against cancer and other debilitating diseases.

Sincerely,

Daniel Passeri, M.Sc., J.D.
Chief Executive Officer

Anish Suri, Ph.D.
President & Chief Scientific Officer

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

FORM 10-K

(Mark One)

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

For the Fiscal Year Ended December 31, 2022

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

For the transition period from _____ to _____

Commission file number: 001-38327

Cue Biopharma, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**47-3324577**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
40 Guest Street Boston, MA	**02135**
(Address of principal executive offices)	**(Zip Code)**

(617) 949-2680
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	CUE	Nasdaq Capital Market

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

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

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

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

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

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

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

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

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

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, as of the last business day of the registrant's most recently completed second fiscal quarter, was approximately $82.1 million (based on the closing price of the registrant's common stock on June 30, 2022 of $2.49 per share).

As of March 13, 2023, the registrant had 43,168,468 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days after the end of the fiscal year ended December 31, 2022. Portions of such proxy statement are incorporated by reference into Part III of this Form 10-K.

CUE BIOPHARMA, INC.
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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements, which are based on certain assumptions and describe our future plans, strategies and expectations, can generally be identified by the use of forward-looking terms such as "believe," "expect," "may," "will," "should," "would," "could," "seek," "intend," "plan," "goal," "project," "estimate," "anticipate," "strategy," "future," "likely" or other comparable terms. All statements, other than statements of historical fact, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements.

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

- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing
- our expectations regarding our ability to fund our projected operating requirements with our existing cash resources and the period in which we expect that such cash resources will enable us to fund such operating requirements;
- our plans to develop our drug product candidates;
- the timing of and our ability to submit applications for, obtain and maintain regulatory approvals for our drug product candidates;
- the potential advantages of our drug product candidates;
- the rate and degree of market acceptance and clinical utility of our drug product candidates, if approved;
- our estimates regarding the potential market opportunity for our drug product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position;
- our ability to identify additional products, drug product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- the impact of government laws and regulations;
- our competitive position;
- developments relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding; and
- the impacts of the COVID-19 pandemic.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. Our actual results and financial condition may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause our actual results and financial condition to differ materially from those indicated in the forward-looking statements include the factors discussed below under the heading "Risk Factor Summary," and the risk factors detailed further in Item 1A., "Risk Factors" of Part I of this Annual Report on Form 10-K.

This report includes statistical and other industry and market data that we obtained from industry publications and research, surveys, and studies conducted by third parties as well as our own estimates. All of the market data used in this report involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys, and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our drug product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research, and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

Any forward-looking statement made by us in this Annual Report on Form 10-K is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

Risk Factor Summary

Investment in our securities involves risk. You should carefully consider the following summary of what we believe to be the principal risks facing our business, in addition to the risks described more fully in Item 1A, "Risk Factors" of Part I of this Annual Report on Form 10-K and other information included in this report. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations.

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

- We are a clinical-stage biopharmaceutical company, have no history of generating commercial revenue, have a history of operating losses, and we may never achieve or maintain profitability.
- We currently do not have, and may never develop, any FDA-approved or commercialized products.
- We are substantially dependent on the success of our drug product candidates, only one of which is currently being tested in a clinical trial, and significant additional research and development and clinical testing will be required before we can potentially seek regulatory approval for or commercialize any of our drug product candidates.
- We have limited experience in conducting clinical trials and no history of commercializing biologic products, which may make it difficult to evaluate the prospects for our future viability.
- The COVID-19 pandemic has, and may continue to, adversely impact our business, including our clinical trials and preclinical studies.
- We plan to seek collaborations or strategic alliances. However, we may not be able to establish such relationships, and relationships we have established may not provide the expected benefits.
- Our collaboration agreement with LG Chem contains exclusivity provisions that restrict our research and development activities.
- We may not be successful in our efforts to identify additional drug product candidates. Due to our limited resources and access to capital, we must prioritize development of certain drug product candidates; these decisions may prove to be wrong and may adversely affect our business.
- We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.
- We rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our drug product candidates and our business could be substantially harmed.
- We rely completely on third parties to manufacture our preclinical and clinical drug supplies for our drug product candidates.
- If we or our licensor is unable to protect our or its intellectual property, then our financial condition, results of operations and the value of our technology and potential products could be adversely affected.
- We will be subject to stringent domestic and foreign regulation in respect of any potential products. The regulatory approval processes of the FDA and other comparable regulatory authorities outside the United States are lengthy, time-consuming and inherently unpredictable. Any unfavorable regulatory action may materially and adversely affect our future financial condition and business operations.
- Even if a potential therapeutic is ultimately approved by the various regulatory authorities, it may be approved only for narrow indications which may render it commercially less viable.
- Even if we receive regulatory approval of our drug product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drug product candidates.
- We have a loan agreement that requires us to meet certain operating covenants and place restrictions on our operating and financial flexibility.

PART I

Item 1. Business

Overview

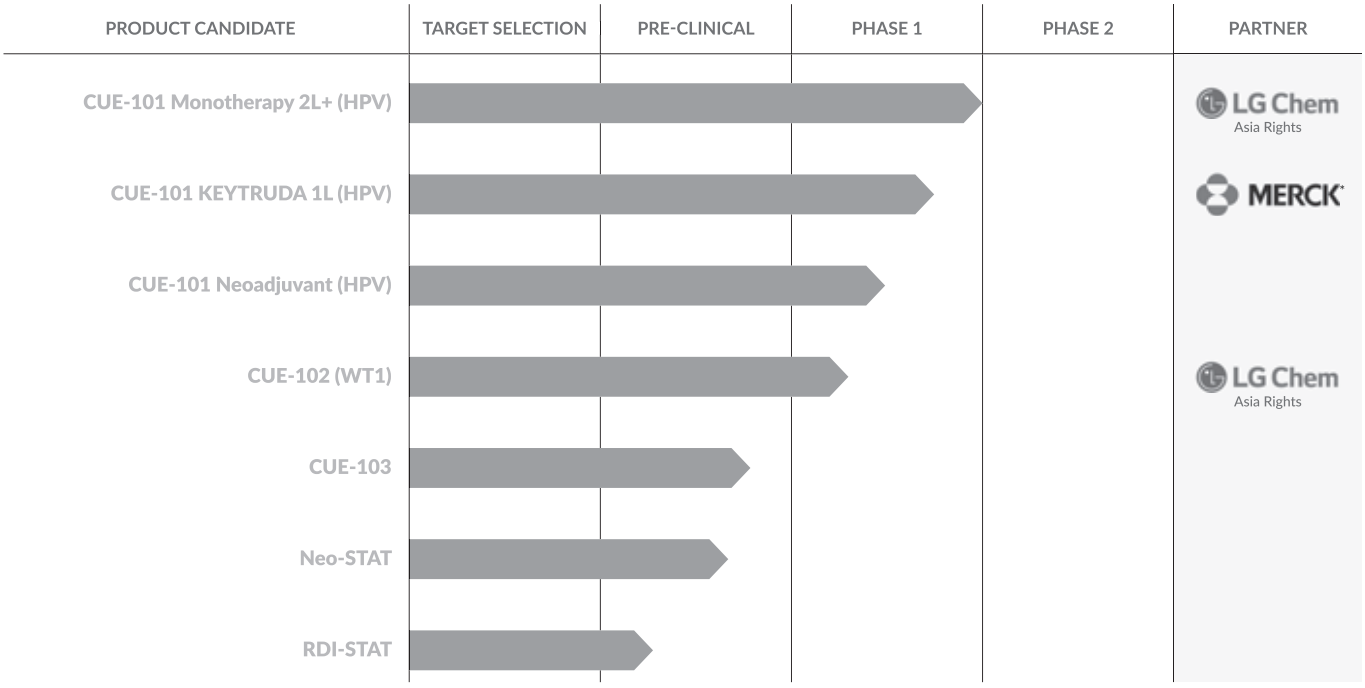
We are a clinical-stage biopharmaceutical company engineering a novel class of injectable biologics to selectively engage and modulate targeted, disease relevant T cells directly within the patient's body. Our vision is to translate nature's cues into protein therapeutics by generating a new class of T cell engagers for selective modulation of disease specific T cells. We believe our proprietary Immuno-STAT™ (*Selective Targeting and Alteration of T Cells*) platform, as described below, will enable us to enhance the potential of the patient's own immune system to restore health while avoiding the deleterious side effects of broad immune activation in the case of cancer and broad immune suppression in the case of autoimmune disease. Our selective immune modulation approach may be deployed for treating cancer, autoimmune diseases and chronic infections. In addition to the highly selective modulation of T cell activity, we believe the core features of Immuno-STATs offer competitive differentiation and advantages, including modularity, manufacturability, and convenient administration that allows for the versatility to treat a broad range of disease.

We believe that we have demonstrated the potential of our engineered Immuno-STAT platform in treating cancer with the preliminary data from our ongoing clinical trial of our lead drug product candidate, CUE-101, representative of the IL-2 based CUE-100 series, the first series from our biologics platform. In response to the current challenges of the financial markets, we have prioritized and strategically focused our internal resources on drug product candidates in our CUE-100 series of Immuno-STATs. The CUE-100 series exploits the selectivity of the T cell receptor, or TCR, combined with rationally engineered interleukin 2, or IL-2, in context of the core Immuno-STAT framework for selective activation of targeted tumor-specific T cells to potentially address a broad range of cancers. In addition to our promising preliminary clinical data pertaining to CUE-101, we continue to develop datasets to elucidate the mechanism of action and further differentiate the CUE-100 series Immuno-STATs from competing approaches. We have also recently observed promising preclinical data pertaining to the potential application of our platform for the treatment of a broad range of autoimmune diseases. Accordingly, we have recently announced the establishment of a strategic collaboration with Ono Pharmaceuticals Co., Ltd., or Ono, focused on the development of CUE-401 for the potential treatment of autoimmune disease through the induction and expansion of regulatory T cells, or Tregs.

Our drug product candidates are in various stages of clinical and preclinical development. We believe the emerging preliminary clinical data for our lead candidate, CUE-101, bolsters our belief that we have developed a potential breakthrough approach for modulating disease relevant T cells directly in the patient's body. However, our activities are also subject to significant risks and uncertainties. We have not yet commenced any commercial revenue-generating operations, have limited cash flows from operations, and will need to access substantial additional capital to fund our growth and ongoing business operations.

Our Immuno-STAT Platform Oncology Pipeline

The pipeline chart below details our current portfolio of oncology assets and their stages of development. We have determined to prioritize and strategically focus on our CUE-101 and CUE 102 oncology programs in our IL-2 based CUE-100 series, and we are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs, as well as our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series.

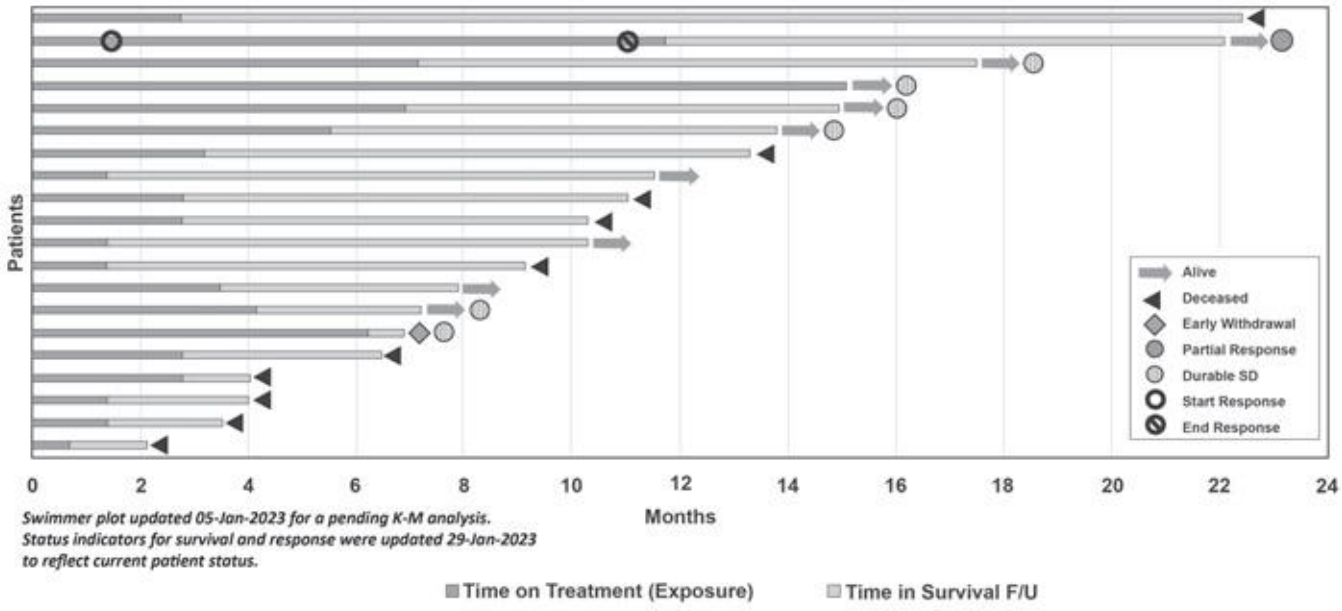


* CUE-101 Combo Trial with KEYTRUDA®

Through a focused and strategic deployment of internal resources, we have made significant progress advancing the IL-2-based CUE-100 series for oncology. CUE-101, representative of the CUE-100 series, is our most advanced clinical stage asset and is being clinically investigated for the treatment of HPV+ head and neck cancer. We completed enrollment of the expansion phase of our monotherapy Phase 1 clinical trial of CUE-101 at the 4 mg/kg recommended Phase 2 dose, or RP2D, for the treatment of second line and beyond, late-stage treatment of recurrent/metastatic head and neck cancer, or R/M HNSCC patients. These patients had received and failed several prior lines of systemic therapy, including chemotherapy and checkpoint inhibitors, or CPIs, such as KEYTRUDA.

CUE-101 has demonstrated evidence of anti-tumor clinical activity as a monotherapy along with a favorable tolerability profile. Of the 19 evaluable patients treated at the RP2D of 4 mg/kg, we observed a confirmed partial response, or PR, lasting for more than 36 weeks and seven patients with durable stable disease, defined as stable disease on at least two consecutive post-treatment scans lasting at least 12 weeks. Of particular note, one of the stable disease patients has had no evidence of tumor growth for over 12 months and has had no detectable evidence of circulating HPV DNA in their blood. This patient continues on treatment in the trial. We have also observed promising preliminary data with respect to CUE-101's pharmacokinetic, or PK, and pharmacodynamic, or PD, profile, as well as biomarker data with respect to circulating HPV DNA as a potential proxy of anti-tumor response. Also of importance is a continuing trend that we have observed of improvement in median overall patient survival, or mOS, which is currently approaching 12 months or greater, and a Kaplan-Meier analysis estimate for mOS (at a 95% confidence interval) of 24.4 months in third line and beyond patients. Data generated from a third-party trial for second line patients receiving check point inhibitor therapy, the current standard of care, demonstrated a mOS of approximately eight months. We continue to follow the patients treated in the monotherapy trial and anticipate this overall survival data to continue to mature throughout 2023.

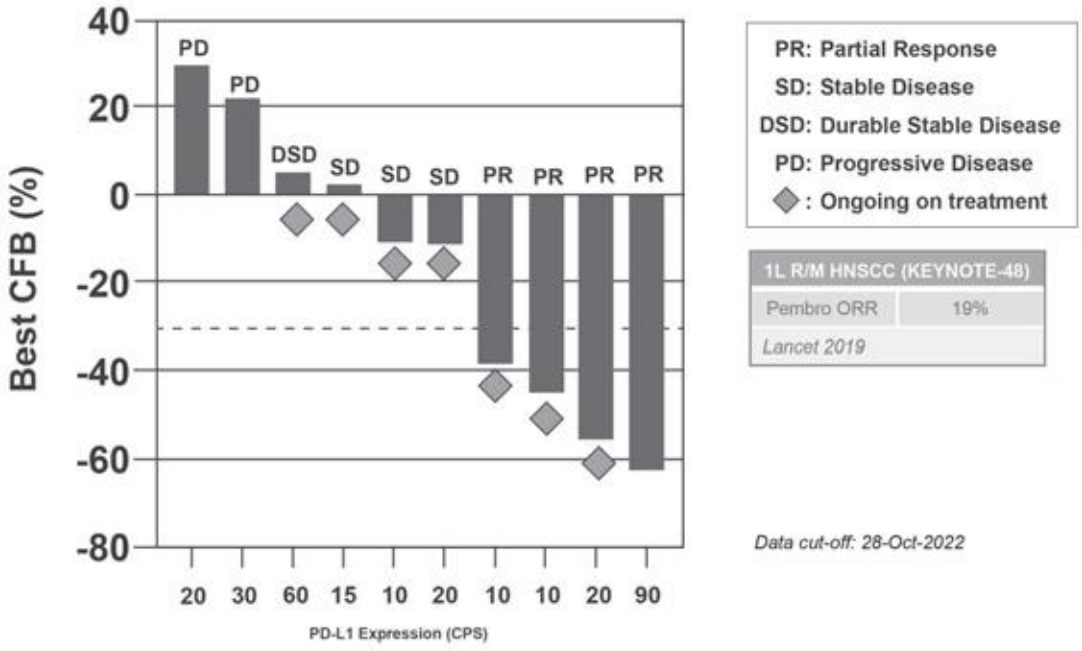
Overall Survival in CUE-101 Phase 1 Monotherapy 4 mg/kg Patients



On October 3, 2022, we received Fast Track Designation of CUE-101 for the treatment of R/M HPV+ HNSCC as a monotherapy and in combination with KEYTRUDA. As the data from the CUE-101 monotherapy and combination with pembrolizumab study matures, we plan to define potential registration paths.

We are currently enrolling patients in a first line, Phase 1 combination trial with Merck Sharp & Dohme Corp.'s, or Merck's, anti-PD-1 therapy KEYTRUDA® (pembrolizumab), the current standard of care for R/M HNSCC. We completed the dose escalation portion of this trial without observing any dose-limiting-toxicity and continue to enroll patients in the expansion phase at the RP2D dose of 4 mg/kg of CUE-101 in combination with the approved dose of KEYTRUDA. The waterfall plot below is an update of the plot that was presented at the 2022 Society for Immunotherapy of Cancer, or SITC, on November 10, 2022, where we reported on the first 10 evaluable patients treated with combination therapy at the RP2D of 4mg/kg of CUE-101 and 200 mg of KEYTRUDA who had at least one post-dose scan at the time of the data cutoff date. At that time we reported two unconfirmed PRs which have subsequently been confirmed, and three patients with stable disease, two of which have become durable, i.e. stable disease lasting greater than 12 weeks. In summary, of these 10 patients, four patients had confirmed ongoing PRs as their best response from baseline demonstrating an initial overall response rate, or ORR, for these first 10 patients of 40%. In addition, one patient demonstrated durable stable disease of greater than 12 weeks and three patients demonstrated stable disease for a clinical benefit rate, to date, of greater than 70% in the first 10 evaluable patients. Importantly, these responses include several patients with low PD-L1 expression (combined positive score, or CPS, less than 20). Notably, tumor reduction from baseline in the four patients with confirmed PRs was between -35% and -60%.

Best Change from Baseline and Response in Patients Treated with 4mg/kg of CUE-101 in Combination with Pembrolizumab



We continue to enroll patients, up to a total of 20 patients at our RP2D of 4mg/kg. We anticipate providing a further update and substantive analysis of this ongoing trial at the upcoming American Society of Clinical Oncology, or ASCO, meeting in June 2023.

We believe the potential combination activity of CUE-101 with KEYTRUDA is likely due to their complementary mechanisms of action, specifically, CUE-101's mechanism of selectively engaging, activating and expanding tumor-specific T cells and KEYTRUDA's mechanism of checkpoint signaling blockade, that allows for the anti-tumor T cells to effectively recognize and kill the tumor cells.

Furthermore, we believe that CUE-101 has the potential to enhance the clinical activity of KEYTRUDA as well as other CPIs, since the presence of expanded tumor-specific T cells is an obligatory pre-requisite for anti-PD-1 therapy. As such, we believe that CUE-101 has the potential to expand patient reach and enhance the therapeutic benefit of CPIs.

Importantly, we believe that the CUE-101 clinical data we have generated to date reduces the risk profile of the entire IL-2 based CUE-100 series because the core framework of the CUE-100 series remains essentially the same for each drug product candidate, except for the targeting peptide epitope within the major histocompatibility complex, or MHC, pocket or the human leukocyte antigen, or HLA. Therefore, with the exception of some protein engineering modifications to ensure stability and manufacturability, the core IL-2 scaffold is a shared molecular feature of all molecules generated within this series (including CUE-102 as described below).

Our second drug product candidate in our CUE-100 series, CUE-102, targets Wilms' Tumor 1 protein, or WT-1, an oncofetal antigen known to be over-expressed in more than 20 different cancers, including both solid tumors (such as colorectal, ovarian, pancreatic and lung) and hematologic malignancies (such as acute myeloid leukemia, multiple myeloma and myelodysplastic syndromes). In April 2022, we received acceptance from the U.S. Food and Drug Administration, or FDA, of our investigational new drug application, or IND, for CUE-102. Based on the premise that CUE-102 shares the same core molecular framework as CUE-101, except for the T cell epitope pertaining to HPV-E7 versus WT-1, its IND was supported by clinical and safety data from the ongoing CUE-101 monotherapy trial and did not require additional IND-enabling toxicology studies. This supports our premise that each CUE-100 series Immuno-STAT molecule provides further de-risking and acceleration of subsequent drug product candidates. With CUE-102 we believe that there is a potential to reach an even larger patient population than for CUE-101 as WT-1 can potentially treat a number of different types of cancer. We have initiated a Phase 1 monotherapy dose-escalation trial with CUE-102 focused on WT-1-positive recurrent/metastatic gastric, pancreatic, ovarian and colorectal cancers at a 1mg/kg dose level. We anticipate completing the dose escalation portion of this Phase 1 clinical trial in mid-2023.

We believe that our CUE-100 series platform can generate multiple therapeutic molecules that selectively target tumor-specific antigens. For example, we have generated proof of concept data with Immuno-STATs targeting mutated driver antigens (such as KRAS) and broadly expressed cancer antigens (such as MAGE-A4). Importantly, the modularity of the platform enables us to generate new drug product candidates targeting tumor antigens that have already been clinically validated, resulting in further potential de-risking and accelerated development of future molecules. For example, in addition to our representative preclinical data with Immuno-STATs targeting the G12V mutated KRAS T cell epitope (including demonstration of selective activation and expansion of T cells expressing G12V-specific T cell receptors), we have also generated Immuno-STAT molecules targeting KRAS T cell epitopes (G12V/D) presented by both the HLA-A03 and -A11 alleles. These additional alleles will potentially enhance patient coverage and market reach.

Furthermore, we have expanded the potential reach of the Immuno-STAT platform to address the heterogeneity and diversity present in many cancers by developing a derivative scaffold of the CUE-100 series containing stable “peptide-less” or “empty” HLA molecules, to which defined peptides of interest may be covalently attached. We refer to this derivative scaffold as Neo-STAT™. Neo-STAT is designed to provide greater flexibility for targeting multiple tumor epitopes, enhancing production efficiencies, and decreasing time and cost associated with manufacturing. We have also generated a derivative biologic designed to address a primary resistance mechanism found in a subset of solid tumors. This escape mechanism is based upon evading immune surveillance through down-regulation of HLA, thereby making the tumor “invisible” to T cells. This derivative of the CUE-100 series, referred to as RDI-STAT, takes advantage of the clinical validation of the CUE-100 series from our Immuno-STAT platform, by deploying an antibody-like targeting moiety binding to tumor specific antigens found on the surface of tumor cells. Through this approach, we believe we may be able to “paint” the tumor with a viral epitope placed within the HLA pocket of the CUE-100 series Immuno-STAT with the potential of then "redirecting" high frequency anti-viral T cells to attack the targeted tumor cells. As noted above, we are seeking partnerships to further develop our Neo-STAT and RDI-STAT programs.

In addition to the CUE-100 series, we have leveraged the modularity of the Immuno-STAT platform to develop additional biologic series outside of oncology, for example, CUE-200, CUE-300 and CUE-400, specifically designed through rational protein engineering to address distinct therapeutic approaches for treating autoimmune disease. The CUE-300 series incorporates the inhibitory PD-L1 co-modulator for selective inhibition of the autoreactive T cell repertoire. The CUE-400 series represents a novel class of bispecific molecules designed to selectively induce and expand Tregs for chronic autoimmune diseases. We recently announced a partnership with Ono supporting the development of CUE-401 for the potential treatment of multiple autoimmune diseases.

Our Business Strategy

Our primary objective is to become a leading biopharmaceutical company developing breakthrough, highly selective and differentiated biologics for safe and effective therapeutic immune modulation directly in patients having high unmet medical need. In order to achieve this objective, we are focused on the following strategies:

Advance our Tumor Antigen-specific IL-2-based CUE-100 series for oncology

- Through CUE-101, as representative and exemplary of our IL-2 based CUE-100 series, we have generated data that demonstrated that IL-2 may be selectively and tolerably delivered to the tumor-specific T cells that are most relevant for anti-tumor immunity. Our approach enables a therapeutic index for IL-2. In contrast, other approaches are focused on systemic delivery of IL-2 variants, with little or no specificity for the activation of the anti-tumor T cells.
- We plan to continue our clinical trials that are designed with a translational approach to demonstrate CUE-101’s ability to selectively engage, activate and expand the patients’ own endogenous HPV16-specific T cells to target, attack and kill tumor cells.
- We plan to expand patient access and potentially enhance clinical outcomes by establishing foundational mechanistic evidence in both our second line and beyond monotherapy Phase 1 clinical trial for HPV16-driven R/M HNSCC and in our Phase 1 combination trial with KEYTRUDA in the first-line R/M HNSCC setting. The expanded patient reach and enhanced therapeutic benefit we have observed to date in our combination trial, supports our underlying premise that our CUE-100 series complements the mechanism of checkpoint blockade by activating and increasing the targeted T cell population directly in the patient's body.

- Through our ongoing and planned clinical trials, we are building a clinical data set to demonstrate the PK/PD, tolerability and anti-tumor effect of CUE-101 as a monotherapy and the potential for clinical synergy in combination with anti-PD-1 therapy in patients with HPV16-driven HNSCC.
- We are also leveraging our modular and versatile Immuno-STAT platform to generate and advance a pipeline of novel Immuno-STATs and Neo-STATs through strategic partnering to enable global patient reach, including, within the CUE-100 series, through our collaboration and strategic territory partnership with LG Chem, Ltd., or LG Chem, for CUE-101 and CUE-102 for Asian markets.

Seek strategic partnerships and collaborations for our programs outside of oncology

- Beyond the IL-2-based CUE-100 series for addressing a broad range of cancers, we also have a pipeline of drug product candidates and programs designed to address significant unmet medical needs for treating serious, life threatening indications, such as autoimmune disease and infectious disease. As a result of our prioritization and strategic focus on oncology, we are actively seeking third party support through partnerships and collaborations, or alternative funding structures to further develop our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series. We recently announced a strategic collaboration and option agreement with Ono to further advance CUE-401, a bispecific protein, specifically designed for the treatment of autoimmune and inflammatory diseases.

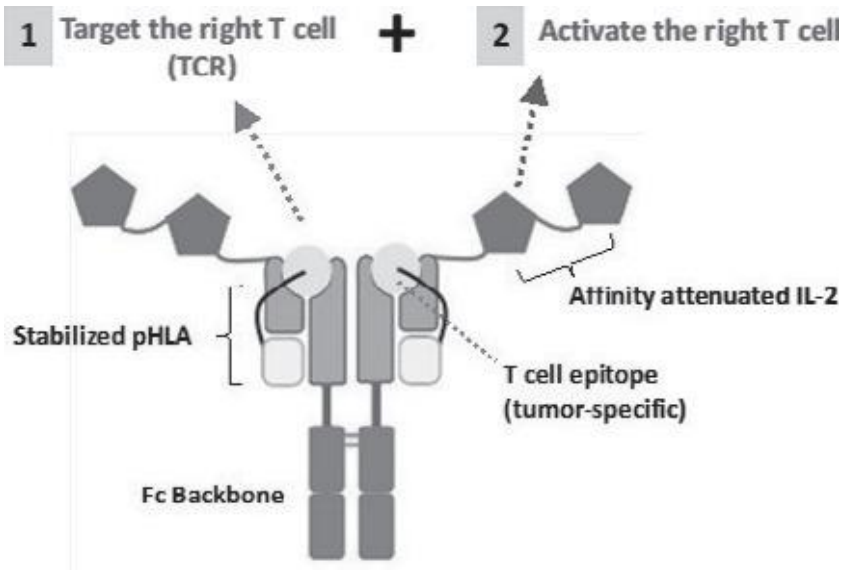
Our Approach

The human immune system is comprised of a number of specialized cell types that collectively function to defend the body against foreign threats as well as the development of cancers. One such specialized cell type, the T cell, is a type of white blood cell that plays a central role in the immune system. During an immune response, T cells are activated via close encounters with a specialized cell type known as the antigen presenting cell, or APC. Prominent APC types include dendritic cells, macrophages, and B cells. The primary function of an APC is to uptake antigens, primarily proteins, catabolize (i.e., break them down into peptides) and display them on their cell-surface in complex with specialized molecules known as MHC molecules or HLA. This critical function of an APC, also referred to as “antigen processing and presentation”, ultimately results in generation of the key molecular substrate – the peptide MHC complex, or pMHC (pMHC will also be used to designate peptide HLA, or pHLA in humans) – that is recognized by the TCR.

The source of antigens for APC processing and presentation is expansive: antigens from pathogens such as viruses, bacteria, mutated proteins from cancers, and others, activate T cells for protective immunity; importantly, antigens from tumor cells are key for robust anti-tumor T cell responses; and antigens from self-tissue are aberrantly recognized by autoreactive T cells that ultimately induce autoimmunity. Hence, the nature of the pMHC complex on the APC establishes the specificity of the T cell response. The intimate interactions between the T cells and APCs occur within a molecular interface known as the immunological or immune synapse wherein the TCR-pMHC engagement as well as additional accessary signals are sensed by T cells resulting in T cell activation or regulation. In essence, the immune synapse allows controlled engagement and selective activation of T cells through the presentation of two distinct signals: Signal 1, TCR engagement of the pMHC; and Signal 2, activating co-stimulatory signals. Ultimately, T cell activation results in the production of the key cytokine IL-2, which serves as a potent autocrine growth factor for the selective clonal expansion of the antigen-specific T cell repertoire.

The core protein framework for the Immuno-STAT platform builds upon our ability to combine the key T cell activation signals into a single molecular scaffold. As shown below, the core framework of a CUE-100 series Immuno-STAT molecule has a stabilized pHLA component that selectively engages those T cells harboring TCRs for tumor-specific peptides, representing Signal 1. In addition, Immuno-STATs contain activating signals (representing Signal 2), including modified IL-2 in the case of the CUE-100 series, that can be selectively delivered to tumor-specific T cells. The core protein framework is built upon an Fc backbone that provides significant structural stability and ease of manufacturing. Modularity is a major strength of the Immuno-STAT framework that allows us to target diverse tumor antigens along with safely delivering a breadth of activating signals. The selective modulation of cancer-relevant T cells, without global immune activation, allows us to achieve therapeutic dosing of highly immune-activating signals such as IL-2. Furthermore, Immuno-STAT molecules are manufactured using established and well-defined processes currently used for antibody and Fc-fusion molecules.

CUE-100 Series Immuno-STAT Framework



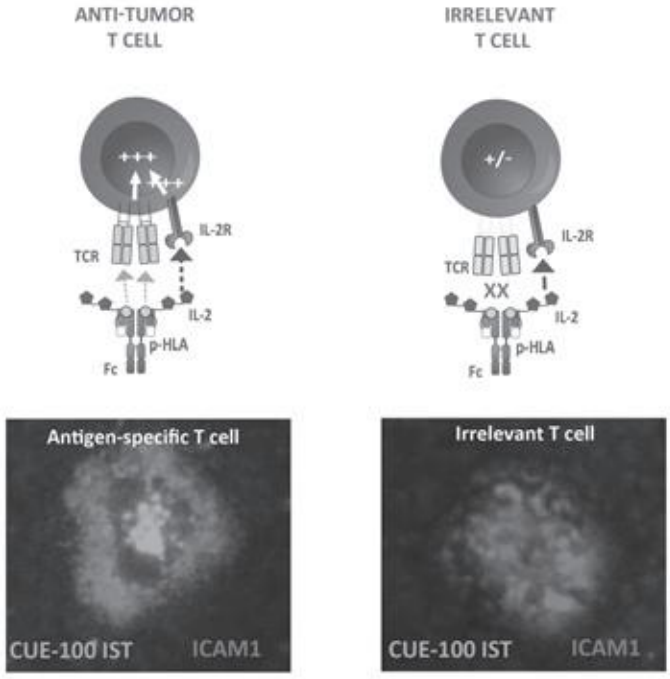
We believe this dual requirement of a specific pMHC interacting with its corresponding TCR, along with a co-stimulatory signal, such as IL-2, is addressed with our CUE-100 series, which drug product candidates are designed to engage the anti-tumor T cells directly with no dependency on the APCs. This is the core focus of the Immuno-STAT platform and its core strategic advantage and differentiation.

The Immuno-STAT: "***Immune Responses, on Cue"***

We are developing a proprietary class of biologic drug product candidates designed to selectively modulate the activity of antigen-specific T cells directly in a patient's body. Through our Immuno-STAT platform, we aim to emulate or "mimic" the signals presented naturally within the immune synapse when the body is mounting an immune response. We seek to accomplish this signaling through the fusion of a TCR targeting pMHC complex (i.e., Signal 1) with co-stimulatory signaling molecules (i.e., Signal 2). This co-engagement of signals through the TCR and co-stimulatory receptor mimics and recapitulates the signals encountered in nature by T cells upon successful interactions with APCs. By design, the Immuno-STATs harness "nature's cues" for antigen specificity, along with appropriate secondary activating or inhibitory signals, to result in targeted T cell modulation.

In May 2020, we entered into a strategic research collaboration with Dr. Michael Dustin and the University of Oxford to determine the molecular mechanisms underlying the activity of our IL-2 based CUE-100 series biologics. Data from this strategic research collaboration were presented at the 2022 Biophysical Society Annual Meeting supporting the hypothesis that Immuno-STAT's concurrent delivery of antigen and IL-2 signals results in robust immune synapse formation on the tumor-specific T cells (as shown below), providing for selective T cell activation. We believe that this data, combined with the cumulative, preliminary clinical data generated to date in our ongoing Phase 1 trial for CUE-101, strongly supports the underlying hypothesis of selective T cell activation via concurrent TCR and IL-2 signaling, with corresponding antitumor activity and clinical benefit.

CUE-100 Series Immuno-STATs Form Immune Synapses on Targeted Tumor-Specific T Cells



During the last decade, there have been substantial efforts made to therapeutically modify the function of immune cells, such as T cells, to either enhance tumor killing in the context of oncology or protect tissue in the context of autoimmune disease. Much of the focus has centered on approaches, including cytokines, cytokine inhibitors, CPIs, and bi-specific antibodies, that rely on systemic, non-specific immune activation for treating cancer or suppression for treating autoimmune disease. Significant challenges for such approaches remain to be addressed, however, regarding specificity, efficacy, and patient safety.

More recently in oncology, adoptive cell therapies (e.g., CAR-Ts, TCR-Ts or ACTs) have shown promise in a process requiring the extraction and modification of T cells from patients, activating, stimulating, and expanding them outside the body (i.e., ex vivo) and then infusing large numbers of cells back into the patients for potential therapeutic benefit. While these approaches have demonstrated some encouraging and impressive clinical responses in several hematologic malignancies, and some solid cancers, they are also associated with significant toxicities, including life threatening cytokine release syndrome and induction of self-reactivity, i.e., autoimmune disease. Moreover, labor-intensive technical requirements and expense associated with individualized T cell extraction, ex vivo amplification or modification, and patient infusion represent significant scaling and cost challenges. This is in addition to the immunodepleting chemotherapy required to condition the patient prior to infusion that may limit the usage of these therapeutic modalities.

Enhancing the Body's Capacity to Fight Cancer

Realizing the potential promise of cancer immunotherapy requires effective and well-tolerated activation and enhancement of the body's intrinsic cancer-fighting capacity. Because an extremely small fraction of a patient's entire T cell repertoire, estimated to be less than 0.1%, is specific to that patient's cancer, non-specific modulation of all T cells via modalities such as rIL-2, CPIs or bispecific T cell engagers will continue to provide sub-optimal outcomes for the majority of patients, unless these modalities can be biased towards the tumor-specific T cells.

By selectively targeting, activating and expanding tumor-specific immune cells directly in the patient's body, we believe our IL-2-based CUE-100 series could solve the foundational problem as to how to selectively activate and amplify only those tumor-specific T cells without broadly activating the vast majority of tumor-irrelevant cells, thus potentially achieving well tolerated and therapeutically effective dose levels.

We believe that our Immuno-STAT and derivative drug product candidates may offer important clinical advantages over competing immunotherapy approaches, including:

- "Off-the-Shelf" and ready to use biologics that specifically target and selectively modulate disease relevant T cells;
- Administration directly into the patient's body without involving extraction and ex-vivo manipulation of T cells (e.g., cell therapy) or rigorous pre- and post- therapy conditioning of the patient;
- Ability to selectively target disease specific T cells and control the quantity and properties of the co-stimulatory signal – in contrast to global activation through systemic, non-selective signaling that is common to therapies such as rIL-2 and bi-specific antibodies;
- Access to a broad set of disease targets and patient populations with unmet medical need;
- Standard delivery format (intravenous or subcutaneous) with a convenient dosing schedule (weekly to monthly) that can be administered by specialists and community-based physicians; and
- Utilization of industry standard development and production process to support a cost-of-goods and supply chain similar to monoclonal antibodies, providing for timely and efficient drug supply.

Immuno therapy Challenges: Exemplified by the Non-selective Nature of IL-2

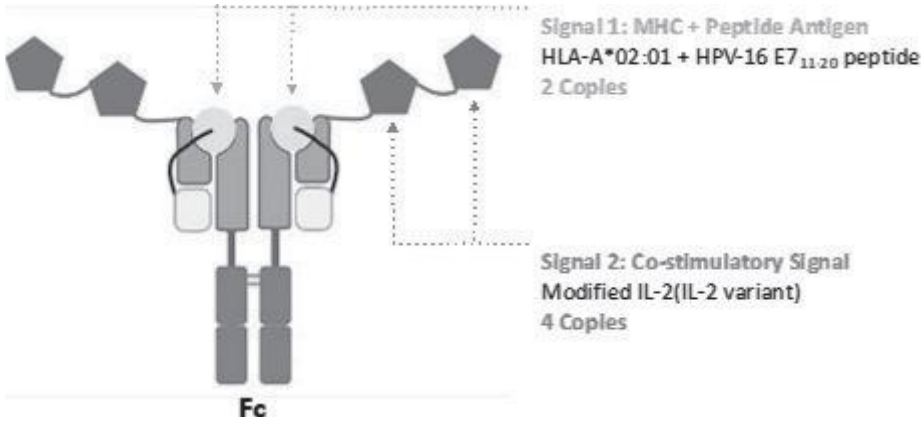
The challenges of effective and well tolerated immunotherapy, exemplified by current IL-2 therapies, center around a lack of selectivity and indiscriminate immune activation, resulting in poor tolerability and limited therapeutic dosing ranges. The primary challenge with wild-type IL-2 for example, as well as the different IL-2 variants in development, is that these molecules will indiscriminately engage the vast majority of the patient's T cells, most of which have no relevance to, or effect on, the patient's cancer.

To realize the full potential of co-stimulatory molecules, such as IL-2 for cancer therapy, we engineered Immuno-STATs to take advantage of the specificity of the TCR allowing for selective activation and expansion of disease relevant T cells with the concurrent engagement of a co-stimulatory molecule, such as IL-2. The CUE-100 series Immuno-STATs to selectively deliver modified IL-2 to tumor-specific T cells while avoiding the systemic activation of all other non-target T cells. Our IL-2 variant is affinity attenuated such that it is designed to selectively act on tumor-specific T cells whose TCR is engaged to the pHLA component of the Immuno-STAT. If the TCR is not engaged, as would be the case with the majority of non-tumor-specific T cells, then the signal from the reduced-affinity IL-2 variant by itself is insufficient to activate the non-tumor-specific T cells. Through the concurrent signaling from the pHLA/TCR complex (signal 1) and IL-2 co-stimulatory signaling (signal 2), we believe we are able to enable the selective activation and amplification of cancer-relevant T cells. In addition, we believe the modularity of the CUE-100 series will allow us to generate diverse therapeutic molecules containing different tumor antigens to target many cancers.

CUE-101

Our lead product candidate from the CUE-100 series, CUE-101, is a fusion protein biologic designed to target and activate antigen-specific T cells to fight HPV-driven cancers. As shown in the figure below, CUE-101 contains an IL-2 variant and a pMHC composed of HLA-A*02:01 complexed with a dominant peptide derived from the human papilloma virus-16 E7 protein, or HPV-16 E7. HPV-16 E7 protein is a primary driver of tumorigenesis and a highly conserved cancer-associated epitope, making it an attractive target for T cell immunotherapy development.

CUE-101 Immuno-STAT Design



We have performed extensive in vitro and in vivo preclinical studies with CUE-101, which have been published in Clinical Cancer Research (Quayle et. al. CUE-101, a Novel HPV16 E7-pHLA-IL-2-Fc Fusion Protein, Enhances Tumor Antigen Specific T Cell Activation for the Treatment of HPV16-Driven Malignancies).

CUE-101 Clinical Development

We have completed enrollment in a Phase 1 monotherapy trial of CUE-101 in second line and beyond patients with HPV+R/M HNSCC and are continuing to dose patients in an ongoing Phase 1 combination trial of CUE-101 with KEYTRUDA in first line patients with HPV+R/M HNSCC. We also initiated an investigator sponsored Phase 1b neoadjuvant trial with Washington University in St. Louis in locally advanced HPV+ HNSCC patients in the second half of 2021.

Treatments for patients with HPV+ cancers represent an important unmet medical need of approximately 25,000 cases of head and neck, cervical and genitoanal cancers in the United States every year, leading to approximately 9,000 deaths annually.

Phase 1 Monotherapy Trial of CUE-101

We completed the dose escalation portion of our Phase 1 monotherapy trial in June 2021 and completed enrollment of 20 patients in an expansion stage Phase 1b at the RP2D of 4 mg/kg. Over the course of the dose-escalation portion of the Phase 1 monotherapy trial, 49 patients were treated across seven dose-escalation cohorts, ranging from 0.06 mg/kg to 8 mg/kg, without a maximum tolerated dose having been identified. We believe this demonstrates the selective activity of CUE-101 and supports our belief that through protein engineering we have designed a biologic for selective engagement and activation of targeted, cancer-relevant T cell populations, potentially sparing patients of the deleterious side effects resulting from indiscriminate activation though systemic IL-2 approaches. As a result of the cumulative data from the dose escalation portion of the Phase 1 trial, we selected 4 mg/kg as the RP2D due to our analysis of PD effect, clinical activity and patient tolerability. In November 2022 at the SITC meeting, we reported that of the 19 evaluable patients dosed at the monotherapy RP2D of 4 mg/kg, we observed a confirmed partial response, or PR, lasting greater than 36 weeks, and an additional six patients with confirmed stable disease, or SD, lasting greater than or equal to 12 weeks. We also reported our observation of an ongoing trend of enhanced overall survival (OS) in these patients receiving CUE-101 monotherapy as a third line or greater treatment. In addition, we reported that we have observed preliminary, robust PK with dose proportional exposure that was sustained across repeat dosing with no evidence of clinically-significant drug clearing antibodies. We have also reported the expansion of targeted, HPV E7 specific disease relevant T cells in the blood of patients and evidence of tumor T cell infiltration on biopsies of tumors following CUE-101 monotherapy treatment. At the RP2D of 4 mg/kg, CUE-101 appears to be well tolerated in the target population. The most common adverse events observed are fatigue, anemia, and decreased lymphocyte counts. All of the serious adverse events and adverse events observed to date are consistent with those that are observed with IL-2 administration or are typical of those observed with CPIs in the treatment of cancer patients. Of note, no events of capillary leak syndrome or severe cytokine storm have been observed to date.

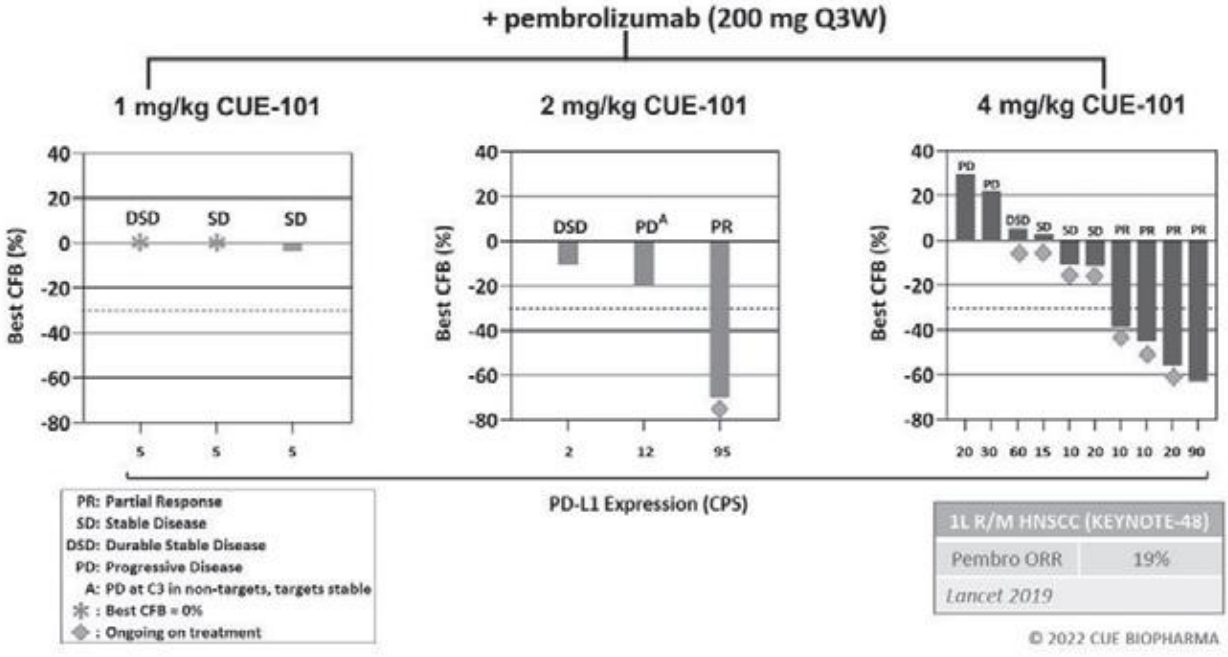
Based on preliminary survival data for the 20 patients treated with 4mg/kg of CUE-101 as a monotherapy, we have observed a continuing trend of improvement in median overall patient survival, or mOS. The mOS is currently approaching 12 months or greater, and a Kaplan-Meier analysis estimate for mOS (at a 95% confidence interval) of 24.4 months. Data generated in a third-party trial for second line patients receiving check point inhibitor therapy, the current standard of care,

demonstrated mOS of approximately 8 months. Although preliminary, we are encouraged that as of November 2022, 11 patients remain on treatment or are in follow-up, and we believe this demonstrates the potential enhancement of survival in patients treated with CUE-101 as a monotherapy. We believe that these data provide mechanistic and clinical support of the premise that the CUE-100 series mechanism of action could complement the mechanism of check point inhibition, thereby potentially expanding patient reach and enhancing therapeutic benefit.

Phase 1 Trial of CUE-101 in Combination with KEYTRUDA

We are also conducting a Phase 1 clinical trial of CUE-101 in combination with KEYTRUDA in the first-line R/M HNSCC treatment setting. We completed the dose escalation portion of this trial without observing any dose-limiting-toxicity and continue to enroll patients in the expansion phase at the RP2D dose of 4 mg/kg of CUE-101 in combination with the approved dose of KEYTRUDA. The waterfall plot below is an update of the graph that was presented at the 2022 Society for Immunotherapy of Cancer (SITC) on November 10, 2022, where we reported on the first 10 evaluable patients treated with combination therapy at the RP2D of 4 mg/kg of CUE-101 and 200 mg of KEYTRUDA who had at least one post-dose scan at the time of the data cutoff date, as well as the six patients treated in cohorts one and two at 1 mg/kg and 2 mg/kg, respectively. In summary, of the first 10 evaluable patients treated with 4 mg/kg of CUE-101 and 200 mg of KEYTRUDA, four patients had confirmed ongoing PRs as their best response from baseline demonstrating an initial overall response rate, or ORR, for these first 10 patients of 40%. In addition, one patient demonstrated durable stable disease of greater than 12 weeks and three patients demonstrated stable disease for a clinical benefit rate, to date, of greater than 70% in the first 10 evaluable patients. Notably, tumor reduction from baseline in the four patients with confirmed PRs was between -35% and -60%. Of note, two of the four patients with PRs had low PD-L1 expression, as evidenced by CPS scores of less than 20. The ORR of 40% observed in the first 10 patients dosed at the RP2D of CUE-101 4 mg/kg and pembrolizumab is encouraging given that the historical ORR of pembrolizumab monotherapy in similar patients was reported to be 19% in the third-party KEYNOTE-48 trial.

Tumor Reductions Observed in Patients Treated With CUE-101 and Pembrolizumab

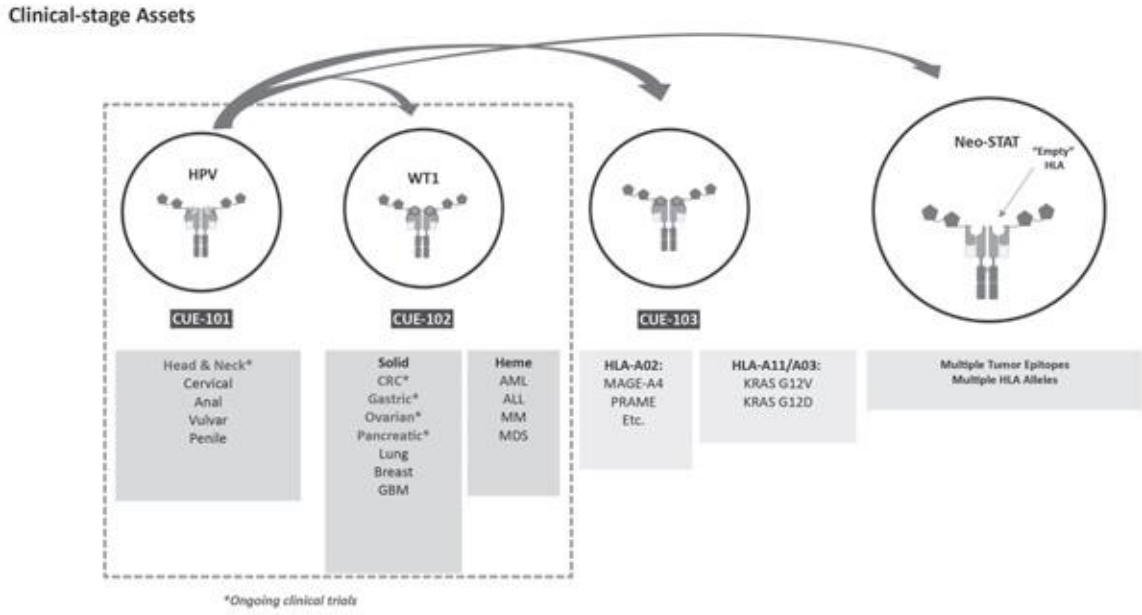


Other Applications of Immuno-STATs to Oncology

We are leveraging our Immuno-STAT platform's modularity and have designed additional Immuno-STAT drug product candidates, including CUE-102 and CUE-103, to expand our reach and further address various therapeutic challenges

of cancer. We have expanded the potential reach of our platform through the modularity of the various Immuno-STAT components, including specific targeting peptides associated with various indications; and targeting distinct global patient populations via diverse HLA alleles. Furthermore, we have designed Immuno-STAT derivatives to address tumor complexity and heterogeneity through the Neo-STAT platform whereby the MHC or HLA complex of an Immuno-STAT is stabilized and produced with an empty peptide binding pocket, allowing for the chemical attachment of defined epitopes post manufacturing. This design affords the opportunity to address tumor heterogeneity by using a mixture of epitopes and potentially provides production scale/efficiencies, flexibility and may have the potential to be "personalized" through sequencing a patient's tumor and defining targeted mutations and cancer-specific epitopes. The modularity of this unique platform provides us the opportunity to generate therapeutic molecules to treat many different cancers.

CUE-100 Series Immuno-STAT Platform Leverages Modularity to Accelerate Development of Multiple Drug Product Candidates

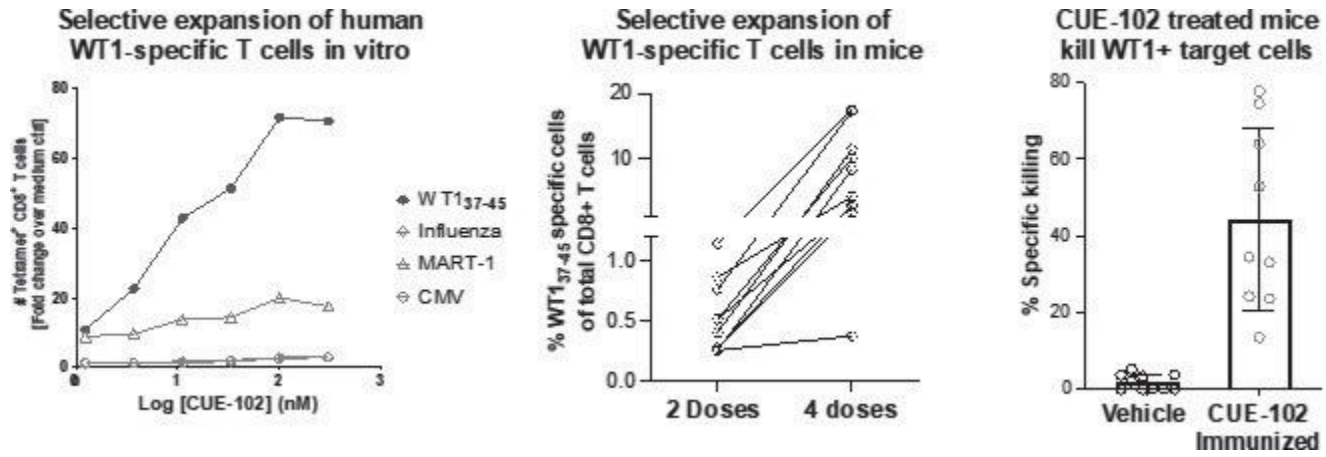


CUE-102

CUE-102 utilizes the same molecular framework as CUE-101 except that the nine amino acid peptide contained in the MHC has been changed to WT-1, an oncofetal antigen known to be over-expressed in more than 20 different cancers, including both solid tumors (such as colorectal, ovarian, pancreatic and lung) and hematologic malignancies (such as acute myeloid leukemia, multiple myeloma and myelodysplastic syndromes). Patients with WT-1 associated cancers represent an important unmet medical need and underscore the opportunity for promising new therapeutics. The IND for CUE-102 was supported by clinical and safety data from the ongoing CUE-101 monotherapy trial. This supports our premise that each CUE-100 series Immuno-STAT drug product candidate provides further de-risking and acceleration of subsequent drug product candidates. We have initiated a Phase 1 monotherapy dose-escalation trial with CUE-102 focused on WT1-positive recurrent/metastatic gastric, pancreatic, ovarian and colorectal cancers at a 1mg/kg dose level, which we believe to be a pharmacologically relevant dose level based on our experience with CUE-101.As a result this starting dose significantly shortens the dose escalation phase of this trial. We anticipate completing the dose escalation portion of this Phase 1 clinical trial in mid-2023.

We have generated a comprehensive preclinical data set with CUE-102 supporting its potential to stimulate anti-tumor immunity, as presented last year at the SITC conference. Our preclinical data generated to date has demonstrated that treatment with CUE-102 led to selective ex-vivo expansion of WT1-specific T cells vs other specific T cells from primary human donors (as shown in the left hand figure below) and in vivo expansion of WT1-specific T cells in HLA-A02 transgenic mice (as shown in the middle figure below). Importantly, the data demonstrated that the T cells activated and expanded via CUE-102 treatment are polyfunctional and capable of killing WT1-presenting target cells (as shown in right hand figure below), both of which are key attributes of a desirable anti-tumor T cell response, and support our belief that CUE-102 treatment can enhance anti-tumor immune responses in patients.

CUE-102: Expansion and Functionality of WT1-Specific T Cells



CUE-103

We have also developed additional CUE-100 series drug product candidates, of which we may designate our next oncology clinical candidate (referred to as CUE-103). We have generated proof of concept data with Immuno-STAT's targeting the KRAS G12V mutation as well as the broadly expressed cancer antigen MAGE-A4. We continue to evaluate these molecules for prioritization in support of future nomination of a preclinical candidate for development with a third party.

Neo-STAT Platform

In addition to the Immuno-STAT biologics described above, engineered as fusion protein biologics, each requiring a dedicated stable cell line for production of good manufacturing practice, or GMP, material, we have engineered a next generation derivative approach, referred to as Neo-STAT™, that we expect could significantly enhance productivity and increase our flexibility, including targeting multiple tumor antigens, neo-antigens and post-translationally modified antigens (e.g., targeting of phospho-peptides from tumor cells). A key focus of the Neo-STAT platform is to generate a "peptide-less" or "empty" MHC pocket within the Immuno-STAT scaffold of the CUE-100 series. We would then deploy standard peptide-conjugation chemistry to covalently attach tumor-specific peptides to the Neo-STAT scaffold. We believe Neo-STAT has the potential to provide enhanced productivities and greater manufacturing flexibility. Importantly, the Neo-STAT framework has the potential to provide scale which would enable us to optimize production efficiencies from a cost, timing, and yield perspective.

We have made significant progress with our Neo-STAT platform, including creation of a master cell line and generation of experimental data demonstrating expansion and activation of primary human T cells with HLA-A02 Neo-STAT molecules deploying different T cell epitopes including tumor antigens (MART-1, WT1, HPV E7) or infectious antigens (CMV, SARS-Cov-2), as examples (see below). A detailed description of the protein engineering of the Neo-STAT platform was previously presented at a 2020 Protein Engineering and Cell Therapy Summit meeting. We plan to continue to progress the Neo-STAT platform with focused efforts designed to demonstrate the versatility of our platform approach.

We believe that our current and planned applications of our Immuno-STAT and Neo-STAT platforms potentially address therapeutic challenges seen with current treatments and may benefit from the ongoing risk-reducing data generated through our ongoing clinical trials of CUE-101, especially as it relates to the tolerability profile of our reduced-affinity IL-2 and novel biologics platform. This is due to the fact that the core framework of the CUE-100 series remains largely the same for each drug product candidate, except for the targeting peptide epitope within the MHC pocket.

In summary, we have focused and deployed our efforts and resources in oncology and have made significant progress demonstrating the potential for our IL-2 based CUE-100 series to selectively stimulate a patient's immune system against cancer with our ongoing trials of CUE-101 addressing HPV+ R/M HNSCC and CUE-102 addressing multiple solid cancer types. We have also implemented a strategy of exploiting the potential applications of the CUE-100 series framework into multiple derivative constructs possessing specific properties and mechanistic attributes to address multiple cancer types and diverse clinical conditions. We believe through our strategic initiatives of first establishing the proof of concept, risk reduction

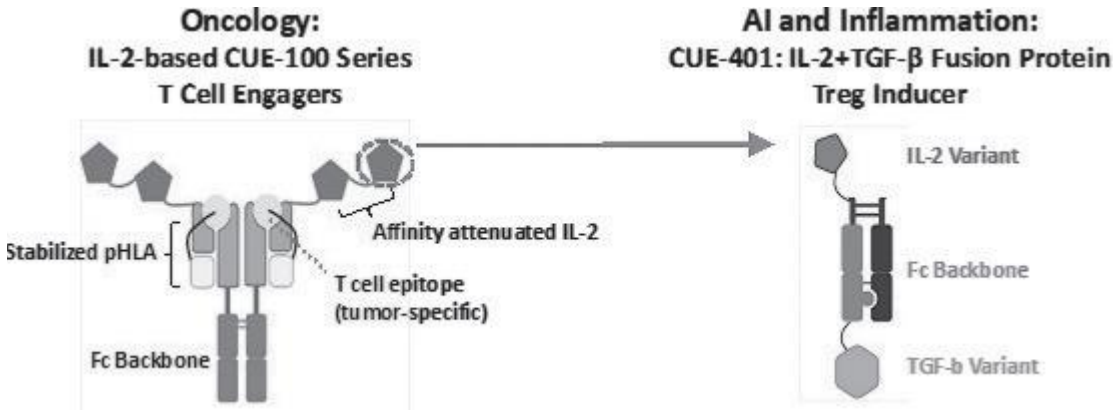
and clinical validation through the clinical development of CUE-101, targeting HPV+ HNSCC in a second line treatment and beyond monotherapy trial, as well as demonstrating potential mechanistic synergy with CPIs in first line patients, we have established a foundation from which we believe we can expand market access and therapeutic reach to patients suffering from a wide range of cancers with future Immuno-STAT drug product candidates and will be seeking partnerships to further develop these potential drug product candidates.

Application of Immuno-STATs Outside of Oncology: CUE-300 and CUE-400

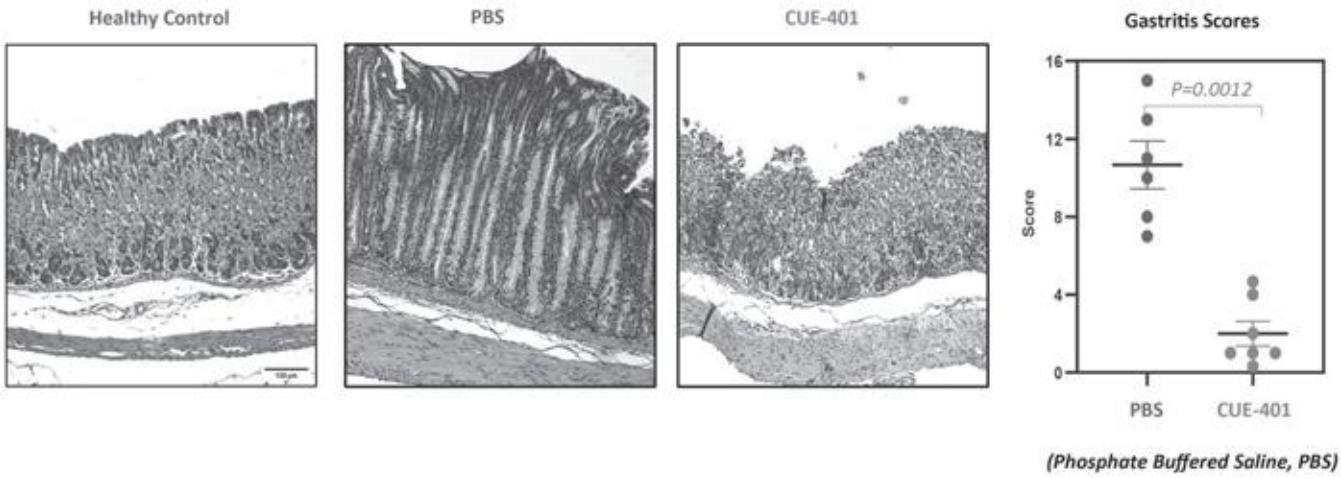
In addition to oncology, we have made recent advances for autoimmune diseases where our core strategy has centered on two major themes: (i) modulating antigen-specific T cells with Immuno-STATs in diseases with restricted or known autoantigens (e.g., type 1 diabetes), and (ii) exploiting a pathway-specific approach via modalities focused on regulatory T cells and other mechanisms that could be broadly applied to autoimmune diseases with unknown or diverse autoantigens. We have generated data for the CUE-300 series that demonstrated the potential for developing a clinical candidate for targeting autoreactive T cells in type 1 diabetes.

Additionally, we expanded our reach into chronic autoimmune diseases having diverse and/or uncharacterized antigens by focusing on regulatory T cells for re-setting immune balance. Our first candidate from this effort, CUE-401, incorporates two key signals, namely IL-2 and TGF-beta, for differentiation and expansion of Tregs. This molecule incorporates the same attenuated IL-2 variant present in CUE-101, which we believe has been de-risked through the favorable tolerability profile observed with CUE-101 in R/M HNSCC patients to date in our ongoing trial, as well as a variant of TGF-beta (see upper figure below). We have generated preclinical datasets in our labs and in collaboration with Dr. Richard DiPaolo of St. Louis University supporting the premise that CUE-401 may be able to expand and induce Tregs. The resulting Tregs are functionally suppressive and maintain a stable phenotype, whereby CUE-401 treatment suppressed the proliferation of self-reactive T cells in a mouse model of autoimmune gastritis. Dr. DiPaolo has also observed the therapeutic potential of CUE-401 in a T cell transfer model of autoimmune gastritis, wherein treatment with CUE-401 led to a prolonged suppression of self-reactive T cells and significantly reduced pathological evidence of disease in the stomachs of treated mice (shown in lower figure below).

CUE-401 Design



CUE-401 treatment resulted in significant protection from tissue destruction



We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series, and there is no guarantee that we will be able to do so on favorable terms or at all.

For example, in February 2022, we announced a collaboration and option agreement with Ono for CUE-401, for the treatment of autoimmune and inflammatory diseases. The strategic collaboration with Ono is an important advancement in our corporate development plan to seek third party support to further develop its CUE-400 series and provides dedicated resources and capabilities to help advance CUE-401 toward the clinic.

Our License Agreement with Einstein

On January 14, 2015, or the Effective Date, we entered into a license agreement, as amended and restated on July 31, 2017 and as amended on October 30, 2018, or the Einstein License, with Albert Einstein College of Medicine, or Einstein, for certain patent rights, or the Patents, relating to our core technology platform for the engineering of biologics to control T cell activity, precision, immune-modulatory drug product candidates, and two supporting technologies that enable the discovery of costimulatory signaling molecules (ligands) and T cell targeting peptides. We hold an exclusive worldwide license, with the right to sublicense, import, make, have made, use, provide, offer to sell, and sell all products, processes and services that use the Patents, including certain technology received from Einstein related thereto, which we refer to as the Licensed Products.

The Einstein License is a royalty-bearing license obligating us to pay a percentage of proceeds received from sales of categories of Licensed Products at low single digit rates. We have also agreed to share a portion of our proceeds that we derive from other agreements, like sublicense agreements, relating to Licensed Products that we may enter into. The percentage of such proceeds that we are required to pay Einstein ranges from the low to mid-teens, depending on how far we have developed a Licensed Product before we enter into an agreement relating to the Licensed Product. These percentages are reduced for sales of Licensed Products in countries where a competing product exists and for products or services involving the use or incorporation of technology received from Einstein relating to synapse for targeted T cell activation molecules, receptor ligand identification or platforms for T cell monitoring. In addition to our obligation to pay royalties based upon a percentage of proceeds from sales of Licensed Products, we have also agreed to pay Einstein annual maintenance fees. The maintenance payments are creditable against any royalty payments we pay under the Einstein License. For the year ended December 31, 2022, there were no payments related to Einstein license maintenance fees under the Einstein License, as they were creditable against actual payments owed to Einstein during the twelve month period.

Under the Einstein License, we are also obligated to make milestone payments corresponding to: (i) approval of the first IND by the FDA or foreign equivalent for a Licensed Product; (ii) approval of any subsequent IND application or foreign equivalent for a “new indication” for a Licensed Product; (iii) initiation of Phase 2 clinical trials or foreign equivalent on a Licensed Product; (iv) initiation of Phase 2 clinical trials or foreign equivalent for a “new indication” for a Licensed Product; (v) initiation of Phase 3 clinical trials or foreign equivalent on a Licensed Product; (vi) initiation of Phase 3 clinical trials or foreign equivalent for a “new indication” for a Licensed Product; (vii) the first commercial sale of a Licensed Product; (viii) the first commercial sale of each “new indication” for one of our previously approved Licensed Products; and (ix) cumulative

sales of certain Licensed Products reaching certain threshold amounts. The aggregate amount of milestone payments made under the Einstein License may equal up to $1.85 million for each Licensed Product and up to $1.85 million for each new indication of a Licensed Product. Additionally, the aggregate amount of one-time milestone payments based on cumulative sales of all Licensed Products may equal up to $5.75 million. As of December 31, 2022, we have made two milestone payments, $150,000 for the approval by the FDA of the IND for CUE-101 and $150,000 for the acceptance of the IND by the FDA for CUE-102.

In addition to our obligations to make the cash payments to Einstein described above, under the Einstein License we issued Einstein 671,572 shares of our Common Stock immediately prior to completion of the initial public offering of our common stock completed on December 27, 2017.

The Einstein License expires upon the expiration of our last obligation to make royalty payments to Einstein, unless terminated earlier under the provisions thereof. Under the Einstein License, we will be obligated to make royalty payments to Einstein, with respect to certain Licensed Products, for the longer of 15 years from the first sale of such products in each country or for the duration of any market exclusivity period granted by a regulatory agency for such product and, with respect to certain Licensed Products sold by sublicensees, the longer of 10 years from the first sale of such products in each country or for so long as the sublicensee agrees to pay royalties on such products. We have the right to terminate the Einstein License at any time upon 60 days' written notice to Einstein; provided, however, that we will lose intellectual property rights related to the Patents if we choose to terminate the Einstein License in this manner. Each party has the right to terminate the Einstein License if the other party is in default or breach of any condition of the Einstein License with a right to cure any such breach within 60 days from receipt of notice of such default or breach, unless the other party has disputed the alleged breach in good faith. Either party can also terminate the Einstein License if the other party voluntarily files for bankruptcy or other similar insolvency proceedings, makes a general assignment for the benefit of creditors, or is the subject of an involuntary bankruptcy petition that is not dismissed within 90 days. If we fail to pay any sum that is due and payable to Einstein within 30 days after receiving written notice of our default from Einstein, then Einstein has the option of terminating the Einstein License unless we pay within 45 days of such notice all delinquent sums with interest.

Einstein may also terminate the Einstein License in the event we are convicted of certain felonies relating to the manufacture or use of Licensed Products.

The Einstein License also obligates us to meet certain due diligence requirements, or the Diligence Milestones, as follows:

- update our research and development plan annually;
- initiate Phase 1 clinical trials on a Licensed Product within a number of years from the Effective Date;
- initiate Phase 2 clinical trials on a Licensed Product within a number of years from the Effective Date;
- initiate Phase 3 clinical trials on a Licensed Product within a number of years from the Effective Date;
- submit an application for FDA approval to market and sell a Licensed Product within a number of years from the Effective Date;
- have our first commercial sale of an FDA Licensed Product within a number of years from the Effective Date; and
- spend a minimum amount per year on product development until our first commercial sale of a Licensed Product.

If we fail to meet any of the Diligence Milestones, Einstein will have the right to terminate the Einstein License if such Diligence Milestone is not satisfied within thirty days from receiving a written notice of default from Einstein. Under certain circumstances and upon prior notice to Einstein, we may have the right to an additional extension of our Diligence Milestones if, despite our commercially reasonable efforts we are not able to satisfy the Phase 2 clinical trial Diligence Milestone or any subsequent Diligence Milestone. As of the date of this report, we have met all required Diligence Milestones.

Our Collaboration Agreement with Merck

On November 14, 2017, we entered into an Exclusive Patent License and Research Collaboration Agreement, or the Merck Collaboration Agreement, with Merck for a partnership to research and develop certain of the Company's proprietary biologics that target certain autoimmune disease indications, or the Initial Indications. We viewed this Merck Collaboration Agreement as a component of our development strategy since it allowed us to advance our autoimmune programs in partnership with a world class pharmaceutical company, while also continuing our focus on our more advanced cancer

programs. The research program outlined in the Merck Collaboration Agreement entailed (1) our research, discovery and development of certain Immuno-STAT drug product candidates up to the point of demonstration of certain biologically relevant effects, or Proof of Mechanism, and (2) the further development by Merck of the Immuno-STAT drug product candidates that have demonstrated Proof of Mechanism, or the Proposed Drug Product Candidates, up to the point of demonstration of all or substantially all of the properties outlined in such Proposed Drug Product Candidates' profiles as described in the Merck Collaboration Agreement.

For the purposes of this collaboration, we granted to Merck under the Merck Collaboration Agreement an exclusive license under certain of our patent rights, including a sublicense of patent rights licensed from Einstein, to the extent applicable to the specific Immuno-STAT drug product candidates that were elected to be developed by Merck. In addition, so long as Merck continued product development on a Proposed Drug Product Candidate, we were restricted from conducting any development activities within the Initial Indication covered by such Proposed Drug Product Candidate other than pursuant to the Merck Collaboration Agreement.

In exchange for the licenses and other rights granted to Merck under the Merck Collaboration Agreement, we received a $2.5 million nonrefundable up-front payment and were eligible to receive additional funding in developmental milestone payments, as well as tiered royalties if all research, development, regulatory and commercial milestones agreed upon by both parties are successfully achieved. We were eligible to earn up to $101 million for the achievement of certain research and development milestones, $120 million for the achievement of certain regulatory milestones and $150 million for the achievement of certain commercial milestones, in addition to tiered royalties on sales, if all pre-specified milestones associated with multiple products across the primary disease indication areas were achieved. The Merck Collaboration Agreement required us to use the first $2.5 million milestone payment we received under the agreement to fund contract research. The amount of the royalty payments was a percentage of product sales ranging in the single digits based on the amount of such sales.

In November 2020, we extended the research collaboration terms of this agreement through December 31, 2021 to support further development and identification of targeted biologics for the treatment of autoimmune disease. Under the terms of this amendment, Merck reimbursed us for specified expenses and provided additional financial research support to further study and develop preclinical biologics with the objective of identifying clinical candidates subject, in each case, to specified maximum amounts, with any amounts in excess of such maximum amounts to be borne by us. On November 18, 2020, we earned a milestone payment related to this amendment in the amount of $300,000. The $300,000 milestone payment was recorded as a contract liability upon receipt. We recognized revenue related to this milestone payment pursuant to our revenue recognition policy in relation to the performance of our obligations related to the development of Immuno-STAT drug product candidates under the arrangement. The research term and financial support of research conducted under the Merck Collaboration Agreement expired on December 31, 2021, and as of December 20, 2022, the Merck Collaboration Agreement was terminated. All rights granted to Merck under the Merck Collaboration Agreement were returned to us with no further obligations to Merck under this agreement.

Our Collaboration Agreement with LG Chem

Effective November 6, 2018, we entered into a Collaboration, License and Option Agreement, or the LG Chem Collaboration Agreement, with LG Chem, related to the development of Immuno-STATs focused in the field of oncology.

Pursuant to the LG Chem Collaboration Agreement, we granted LG Chem an exclusive license to develop, manufacture and commercialize our lead product, CUE-101, as well as Immuno-STATs that target T-cells against two additional cancer antigens, or Drug Product Candidates, in Australia, Japan, Republic of Korea, Singapore, Malaysia, Vietnam, Thailand, Philippines, Indonesia, China (including Macau and Hong Kong) and Taiwan, which we refer to collectively as the LG Chem Territory. We retain rights to develop and commercialize all assets included in the LG Chem Collaboration Agreement in the United States and in global markets outside of the LG Chem Territory. Under the LG Chem Collaboration Agreement, we will engineer the selected Immuno-STATs for up to three alleles, which are expected to include the predominant alleles in the LG Chem Territory, thereby enhancing our market reach by providing for greater patient coverage of populations in global markets, while LG Chem will establish a chemistry, manufacturing and controls, or CMC, process for the development and commercialization of selected Drug Product Candidates. In addition, LG Chem has the option to select one additional Immuno-STAT for an oncology target, or an Additional Immuno-STAT, for an exclusive worldwide development and commercialization license. On December 18, 2019, we and LG Chem entered into a global license and collaboration agreement, which was amended on November 5, 2020. We refer to such agreement, as amended, as the Global License and Collaboration Agreement. The Global License and Collaboration Agreement supersedes the provisions of the LG Chem Agreement related to LG Chem's option for an Additional Immuno-STAT but generally does not become effective unless and

until LG Chem exercises its option, other than certain select provisions including the length of the option period and representations, warranties and covenants of the parties. On April 30, 2021, LG Chem's option pursuant to the Global License and Collaboration Agreement expired. We will retain an option to co-develop and co-commercialize the additional program worldwide.

Under the terms of the LG Chem Collaboration Agreement, LG Chem paid us a $5.0 million non-refundable, non-creditable upfront payment and purchased approximately $5.0 million of shares of our common stock at a price per share equal to a 20% premium to the volume weighted-average closing price per share over the 30 trading day period immediately prior to the effective date of the LG Chem Collaboration Agreement. We are also eligible to receive additional aggregate payments of approximately $400 million if certain research, development, regulatory and commercial milestones are successfully achieved. On May 16, 2019, we earned a $2.5 million milestone payment for the FDA's acceptance of the IND for our lead drug product candidate, CUE-101, pursuant to the LG Chem Collaboration Agreement. On December 7, 2020, we earned a $1.25 million milestone payment on the selection of a preclinical candidate pursuant to the LG Chem Collaboration Agreement. On November 23, 2021, we earned a $3.0 million milestone payment on the confirmation of Collaboration Product Candidate. In addition, the LG Chem Collaboration Agreement also provides that LG Chem will pay us tiered single-digit royalties on net sales of commercialized Product Candidates, or Collaboration Products, in the LG Chem Territory on a product-by-product and country-by-country basis, until the later of expiration of patent rights in a country, the expiration of regulatory exclusivity in such country, or ten years after the first commercial sale of a Collaboration Product in such country, subject to certain royalty step-down provisions set forth in the LG Chem Collaboration Agreement. In addition, the LG Chem Collaboration Agreement also provides that LG Chem will pay us tiered single-digit royalties on net sales of commercialized Drug Product Candidates, or Collaboration Products, in the LG Chem Territory on a product-by-product and country-by-country basis, until the later of expiration of patent rights in a country, the expiration of regulatory exclusivity in such country, or ten years after the first commercial sale of a Collaboration Product in such country, subject to certain royalty step-down provisions set forth in the LG Chem Collaboration Agreement.

Pursuant to the LG Chem Collaboration Agreement, the parties will share research costs related to Collaboration Products, and LG Chem will provide CMC process development for selected Drug Product Candidates and potentially additional downstream manufacturing capabilities, including clinical and commercial supply for Collaboration Products. In return for performing CMC process development, LG Chem is eligible to receive low-single digit percentage royalty payments on the sales of Collaboration Products sold in all countries outside the LG Chem Territory. As of December 31, 2022, we recorded approximately $19.6 million in collaboration revenue related to this agreement since inception. The majority of the research phase of the collaboration agreement was substantially complete on March 31, 2022.

The LG Chem Collaboration Agreement includes various representations, warranties, covenants, indemnities and other customary provisions. LG Chem may terminate the LG Chem Collaboration Agreement for convenience or change of control of us on a program-by-program, product-by-product or country-by-country basis, or in its entirety, at any time following the notice period set forth in the LG Chem Agreement. Either party may terminate the LG Chem Agreement, in its entirety or on a program-by-program, product-by-product or country-by-country basis, in the event of an uncured material breach. The LG Chem Collaboration Agreement is also terminable by either party (i) upon the bankruptcy, insolvency or liquidation of the other party or (ii) for certain activities involving the challenge of certain patents controlled by the other party. Unless earlier terminated, the LG Chem Collaboration Agreement will expire on a product-by-product and country-by-country basis upon the expiration of the applicable royalty term.

To date, LG Chem has selected one additional cancer antigen, WT1, which is the focus of the CUE-102 research program. We are currently developing two Collaboration Products with LG Chem pursuant to this agreement.

Our Intellectual Property

We believe that our current patents and patent applications and any future patents and other proprietary rights that we own, or control through licensing, are and will be essential to our business. We believe that these intellectual property rights will affect our ability to compete effectively with others. We also rely and will rely on trade secrets, know-how, continuing technological innovations and licensing opportunities to develop, maintain and strengthen our competitive position. We seek to protect these, in part, through confidentiality agreements with certain employees, consultants, advisors and other parties. Our success will depend in part on our ability, and the ability of our licensors, to obtain, maintain (including making periodic filings and payments) and enforce patent protection for our/their intellectual property, including those patents and patent applications to which we have secured exclusive rights.

As of December 31, 2022, we owned or had licensed 91 issued patents (including 11 issued U.S. patents), 57 pending patent applications in the United States (including 21 pending U.S. provisional patent applications), 18 pending international PCT applications and 229 pending foreign patent applications intended to protect the intellectual property underlying our technology. Our patent applications describe certain features of our technologies, including our Immuno-STAT platform, our Neo-STAT platform, CAR-T and ex-vivo applications of our Immuno-STAT platform, our RDI-STAT platform, our CUE-400 Series platform, including CUE-401, as well as specific biologic molecules, drug product candidates and methods of treatment using our Immuno-STATs. We plan to spend considerable resources and focus in the future on obtaining U.S. and foreign patents. We have and will continue to actively protect our intellectual property. No assurances can be given that any of our patent applications will result in the issuance of a patent or that the examination process will not require us to narrow our claims. In addition, any issued patents may be contested, circumvented, found unenforceable or invalid, and we may not be able to successfully enforce our patent rights against third parties. No assurance can be given that others will not independently develop a similar or competing technology or design around any patents that may be issued to us. We intend to expand our international operations in the future and our patent portfolio, copyright, trademark and trade secret protections may not be available or may be limited in foreign countries.

Each of our patents, if and when granted, will generally have a term of 20 years from its respective U.S. non-provisional priority filing date, subject to available extensions. They are thus set to expire no earlier than dates ranging from 2033 to 2042, although patents that specifically cover Cue products will expire no earlier than December 2037, subject to available extensions.

Competition

While we believe that our drug product candidates, technology, knowledge and experience provide us with significant competitive advantages, we face competition from established and emerging pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others, who may have drug product candidates in further stages of development than ours.

Oncology Competition

We compete with other companies working to develop cytokines as cancer immunotherapies, as well as those developing other immunotherapeutic modalities, including monoclonal antibodies, bi-specific antibodies, antibody-drug conjugates, cell therapies, oncolytic viruses, and vaccines with application in treating patients living with cancer. Potential competitors in the cytokine-based therapy space include Alkermes, Inc., Asher Bio, BioNTech SE, Medicenna Therapeutics, Moderna, Inc., and Roche Holding AG. In the cell therapy space, potential competitors include Adaptimmune Therapeutics PLC, Bristol-Myers Squibb, Iovance Biotherapeutics, Gilead Sciences, Janssen Pharmaceuticals, and Novartis AG, and in the checkpoint inhibitor space potential competitors include Astra-Zeneca, Bristol-Myers Squibb, Merck & Co., and Roche Holding AG.

We believe that our approach provides us with a competitive advantage through selective delivery of immune activating signals, coupling engineered cytokines (i.e., IL-2) to a targeting moiety (i.e., peptide-MHC complex) for enhanced activation of cancer-specific CD8+ T cells.

Autoimmune Competition

We compete with other companies working to develop cytokines to restore immune balance, as well as those developing other therapeutic modalities, including monoclonal antibodies, bi-specific antibodies, cell therapies, and vaccines with application in treating patients living with autoimmune disease. Potential competitors in the cytokine-based therapy space include Amgen, Bristol-Myers Squibb, Eli Lilly and Company, Merck & Co., and Sanofi S.A. In the regulatory T cell therapies space, potential competitors include Abata Therapeutics, Coya Therapeutics, Sangamo Therapeutics, and Sonoma Biotherapeutics.

Many of our competitors have greater financial, technical and human resources than we do. Additionally, many competitors have greater experience in product discovery and development, obtaining FDA and other regulatory approvals, and commercialization capabilities, which may provide them with a competitive advantage.

We expect any drug product candidate that we commercialize, either independently or with our strategic partners, will compete with existing, market-leading products and believe that our ability to compete will depend on our ability to execute on the following objectives:

- design, develop and commercialize products that are superior to other products in the market in terms of, among other things, safety, efficacy, convenience, or price;

- obtain patent and/or other proprietary protection for our processes and drug product candidates;
- obtain required regulatory approvals;
- obtain favorable reimbursement, formulary and guideline status; and
- collaborate with others in the design, development and commercialization of our products.

Established competitors may invest heavily to discover and develop novel compounds that could make our drug product candidates obsolete. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and/or safety in order to obtain approval, to overcome price competition and to be commercially successful. If we are not able to compete effectively, our business will not grow and our financial condition and operations will suffer.

Government Regulation and Licensure of Products

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, sales, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products, including biological products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Licensure and Regulation of Biologics in the United States

In the United States, our product candidates are regulated as biological products, or biologics, under the Public Health Service Act, or the PHSA, and the Federal Food, Drug and Cosmetic Act, or the FDCA, and its implementing regulations and guidance. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. The failure to comply with the applicable U.S. requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may subject a sponsor to delays in the conduct of the study, regulatory review and approval, and/or administrative or judicial sanctions. A sponsor seeking approval to market and distribute a new biologic in the United States generally must satisfactorily complete each of the following steps:

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations and standards and other applicable regulations;
- completion of the manufacture, under current Good Manufacturing Practices, or GMP, conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing;
- design of a clinical protocol and submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency, and purity of the product candidate for each proposed indication, in accordance with current Good Clinical Practices, or GCP;
- preparation and submission to the FDA of a Biologic License Application, or BLA, for a biologic product requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labelling;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with GMP

requirements and to assure that the facilities, methods, and controls are adequate to preserve the product's identity, strength, quality, and purity, and, if applicable, the FDA's current good tissue practice for the use of human cellular and tissue products;

- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCPs and the integrity of clinical data in support of the BLA;

- payment of user Prescription Drug User Free Act, or PDUFA, securing FDA approval of the BLA and licensure of the new biologic product; and

- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies required by the FDA.

Preclinical Studies

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

The IND Process

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin or recommence.

As a result, submission of the IND may result in the FDA not allowing the trials to commence or allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND process, it may choose to impose a partial or complete clinical hold. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls. This order issued by the FDA would delay either a proposed clinical study or cause suspension of an ongoing study, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed. This could cause significant delays or difficulties in completing planned clinical studies in a timely manner.

Expanded Access to an Investigational Drug for Treatment Use

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

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

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or the Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Although these requirements were rolled out over time, they have now come into full effect. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a manufacturer to make its investigational products available to eligible patients as a result of the Right to Try Act.

Human Clinical Trials in Support of a BLA

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under study protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the trial as support for an IND or application for marketing approval. Specifically, the FDA requires that such trials be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from subjects. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for clinical trials in the United States.

Further, each clinical trial must be reviewed and approved by an IRB either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or the clinical trial sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, or DSMB. This group may recommend continuation of the study as planned, changes in study conduct, or cessation of the study at designated check points based on certain available data from the study to which only the DSMB has access. Finally, research activities involving infectious agents, hazardous chemicals, recombinant DNA, and genetically altered organisms and agents may be subject to review and approval of an Institutional Biosafety Committee in accordance with U.S. National Institutes of Health, or NIH, Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may be required after approval.

- *Phase 1* clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion, and pharmacodynamics in healthy humans or, on occasion, in patients, such as cancer patients.

- *Phase 2* clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials.

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

In some cases, the FDA may approve a BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement or to request a change in the product labeling. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In March 2022, the FDA released final guidance entitled "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics," which outlines how developers can utilize an adaptive trial design commonly referred to as a seamless trial design in early stages of oncology biological product development (i.e., the first-in-human clinical trial) to compress the traditional three phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts are included in IND applications and assessed by the FDA. Expansion cohort trials can potentially bring efficiency to product development and reduce developmental costs and time.

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

Finally, sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. The NIH's Final Rule on registration and reporting requirements for clinical trials became effective in 2017. Although the FDA has historically not enforced these reporting requirements due to the long delay of the U.S. Department of Health and Human Services, or HHS, in issuing final implementing regulations, the FDA has issued several Notices of Noncompliance to manufacturers since April 2021.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, a BLA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The sponsor, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the sponsor may request an amendment to the plan at any time.

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

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The FDA is required to send a Pediatric Research Equity Act, or PREA, Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA.

Compliance with GMP Requirements

In connection with its review of a BLA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug or biologic undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with GMPs and other laws. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. The FDA's regulations also require, among other things, the investigation and correction of any deviations from GMP and the imposition of reporting and documentation requirements upon the sponsor and any third-party manufacturers involved in producing the approved product.

Submission and Filing for Review of a BLA

The results of product candidate development, preclinical testing, and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a BLA requesting a license to market the product. The BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee. Under federal law, the submission of most BLAs is subject to an application user fee, which for federal fiscal year 2023 is $3,242,026 for an application requiring clinical data. The sponsor of a licensed BLA is also subject to an annual program fee, which for federal fiscal year 2023 is $393,933. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

The FDA conducts a preliminary review of all applications within 60 days of receipt and must inform the sponsor at that time or before whether an application is sufficiently complete to permit substantive review. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File determination to the sponsor. The FDA may request additional information and studies, and the application must be resubmitted with the additional information. The resubmitted application is subject to review before the FDA accepts it for filing.

Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under the PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the sponsor, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs. The review process may often be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by

three months if the FDA requests or if the sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

In connection with its review of an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with a submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with current GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an application, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the data submitted in support of the application. With passage of FDORA, Congress clarified FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to FDA as well as other persons holding study records or involved in the study process.

The FDA may also refer the application to an advisory committee for review, evaluation, and recommendation as to whether the application should be approved. In particular, the FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates, and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Decisions on BLAs

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a Complete Response Letter, or CRL, or an approval letter. To reach this determination, the FDA must determine whether there is substantial evidence that the product is effective and that expected benefits of the proposed product outweigh its potential risks to patients. This assessment is informed by the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks.

If the application is not approved, the FDA will issue a complete response letter, or CRL, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a CRL may submit to the FDA information that represents a complete response to the issues identified by the FDA. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by a sponsor in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission. The FDA will not approve an application until issues identified in the complete response letter have been addressed. For those seeking to challenge FDA's CRL decision, the agency has indicated that sponsors may request a formal hearing on the CRL or they may file a request for reconsideration or a request for a formal dispute resolution.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications.

The FDA may limit the approved indications for use of the product. It may also require that contraindications, warnings or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patent registries.

The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Expedited Review Programs

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

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

- *Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.
- *Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention compared to marketed products. FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.
- *Accelerated approval.* Biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials. With passage of FDORA, in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to: require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded; require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to FDA every six months (until the study is completed); and use expedited procedures to withdraw accelerated approval of a new drug application, or NDA, or BLA after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.
- *Regenerative advanced therapy.* With passage of the Cures Act in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

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

Project Optimus

Project Optimus is an initiative of the Oncology Center of Excellence at the FDA. This project focuses on dose optimization and dose selection in oncology drug development, and whether the current paradigm based on cytotoxic chemotherapeutics leads to doses and schedules of molecularly targeted therapies that provide more toxicity without additional efficacy, among other things. In Project Optimus, drug developers have the opportunity to meet with the FDA's Oncology Review Divisions early in their development programs, well before conducting trials intended for registration, to discuss dose-finding and dose optimization. The program thus allows sponsors to develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials, with the objective of performing these studies as early as possible in the development program to bring promising new therapies to patients.

Real-Time Oncology Review of Supplemental NDAs

Through its Oncology Center for Excellence, or OCE, the FDA has established two pilot programs allowing for real-time review of supplemental applications for previously approved oncology products. This approach will allow FDA to evaluate clinical data as soon as the results of a clinical trial become available with the objective of reviewing and approving a new indication soon after a sponsor files the application. The first of these pilot programs, Real-Time Oncology Review, or RTOR, focuses on early submission of data that are the most relevant to assessing the product's safety and effectiveness. RTOR allows the FDA to review much of the data earlier, after the clinical trial results become available and the database is locked, but before the information is formally submitted to the agency.

The FDA has established several criteria to determine whether a supplemental application may be selected for RTOR. Those criteria include whether: the investigational product is likely to demonstrate substantial improvements over available therapy; the study design is straight forward, as determined by the review division and the OCE; the endpoints can be easily interpreted. Applications with chemistry, manufacturing and control formulation changes and supplements with pharmacology/toxicology data are excluded from RTOR. In addition, submissions with greater complexity, including those with companion diagnostics, may also be excluded for the purposes of the pilot program. On the basis of these criteria, the appropriate FDA review division and OCE management will jointly decide whether the application can be selected for the RTOR pilot program.

If the FDA determines that RTOR is an appropriate review pathway, the sponsor can send pre-submission data to the agency under the original application two to four weeks after all patient data have been entered and locked in the database, and the sponsor is ready to request FDA approval. The package should also include key raw and derived datasets, including safety/efficacy tables and figures, study protocol and amendments, and a draft of the package insert. The sponsor must also submit key results, analysis, and datasets for other disciplines, if applicable. The FDA will then evaluate these materials for sufficiency and integrity so that it can analyze the data to properly address key regulatory questions. By the time the sponsor submits the application to the FDA, the review team will have completed the analysis and be familiar with the data, and can conduct a more efficient, timely, and thorough review.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA have imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including GMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money, and effort in the areas of production and quality control to maintain compliance with GMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency, and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or

failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Pharmaceutical products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. Although health care providers may prescribe products for off-label uses in their professional judgment, drug manufacturers are prohibited from soliciting, encouraging or promoting unapproved uses of a product. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a biologic.

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

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

Orphan Drug Designation and Exclusivity

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the United States or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the biologic for the disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation qualifies a company for tax credits and market exclusivity for seven years following the date of the product’s marketing approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan when it receives orphan drug designation from the Office of Orphan Products Development at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan

drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first drug. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

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

The period of exclusivity begins on the date that the marketing application is approved by the FDA. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. Under Omnibus legislation signed by the then President of the United States on December 27, 2020, the requirement for a product to show clinical superiority applies to drug products that received orphan drug designation before enactment of amendments to the FDCA in 2017 but have not yet been approved by FDA.

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

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of regulatory exclusivity to the term of any existing regulatory exclusivity, including orphan exclusivity, for biologic products. This six-month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Biosimilars and Exclusivity

The 2010 Patient Protection and Affordable Care Act, which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or the BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. A biosimilar is a biological product that is highly similar to an existing FDA-licensed "reference product." To date, the FDA has approved a number of biosimilars and the first interchangeable biosimilar product was approved on July 30, 2021 and a second product previously approved as a biosimilar was designated as interchangeable in October 2021.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. In December 2022, Congress clarified through FDORA that FDA may approve multiple first

interchangeable biosimilar biological products so long as the products are all approved on the first day on which such a product is approved as interchangeable with the reference product.

An application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity, and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. There have been recent government proposals to reduce the 12-year reference product exclusivity period, but none has been enacted to date. At the same time, since passage of the BPCIA, many states have passed laws or amendments to laws, which address pharmacy practices involving biosimilar products.

Patent Term Restoration and Extension

A patent claiming a new biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of the IND clearing the clinical investigation involving human beings and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

FDA Approval of Companion Diagnostics

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

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

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

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import,

and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution.

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

A clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the Quality System Regulation, which covers the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 became effective in the European Union and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union, or EU Member State, will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the European Medicines Agency, or EMA, and available to clinical trial sponsors, competent authorities of the EU Member States and the public.

The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU member states in which an application for authorization of a clinical trial has been submitted, or concerned member states. Part II is assessed separately by each

concerned member state. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned member state. However, overall related timelines will be defined by the Clinical Trials Regulation.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

As in the U.S., similar requirements for posting clinical trial information are present in the E.U. (EudraCT) website: https://eudract.ema.europa.eu/ and other countries.

PRIME Designation in the EU

In March 2016, the EMA, launched an initiative to facilitate development of drug product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority Medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of drug product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies are appointed early in the PRIME scheme facilitating increased understanding of the product at the EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Pediatric Studies

Sponsors developing a new medicinal product must agree upon a Pediatric Investigation Plan, or PIP, with the EMA's pediatric committee, or PDCO, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies (e.g., because the relevant disease or condition occurs only in adults). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted by the PDCO of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults, in which case the pediatric clinical trials must be completed at a later date.

Marketing Authorization

To obtain a marketing authorization for a product under the European Union regulatory system, a sponsor must submit an MAA, either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in European Union Member States (decentralized procedure, national procedure, or mutual recognition procedure). A marketing authorization may be granted only to a sponsor established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, a sponsor must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. Manufacturers must demonstrate the quality, safety, and efficacy of their products to

the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

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

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent Term Extensions in the European Union and Other Jurisdictions

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

Periods of Authorization and Renewals

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To that end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization that is not followed by the placement of the drug on the EU market (in the case of the centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

Regulatory Requirements after Marketing Authorization

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include compliance with the European Union's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's GMP requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities, and

controls used in manufacturing, processing and packing of drugs to assure their safety and identity. Finally, the marketing and promotion of authorized products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union under Directive 2001/83EC, as amended.

Orphan Drug Designation and Exclusivity

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the drug in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the sponsor must demonstrate that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the drug will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized European Union marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity.

Pediatric Exclusivity

Products that are granted a marketing authorization with the results of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) even where the trial results are negative. In the case of orphan medicinal products, a two year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Approval of Companion Diagnostic Devices

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

Separately, the regulatory authorities in the EU also adopted a new In Vitro Diagnostic Regulation, or IVDR, (EU) 2017/746, which became effective in May 2022. The new regulation replaces the In Vitro Diagnostics Directive (IVDD) 98/79/EC. Manufacturers wishing to apply to a notified body for a conformity assessment of their in vitro diagnostic medical device had until May 2022 to update their Technical Documentation to meet the requirements and comply with the new, more stringent Regulation. The regulation will, among other things: strengthen the rules on placing devices on the market and reinforce surveillance once they are available; establish explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance, and safety of devices placed on the market; improve the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number; set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the European Union; and strengthen rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom's withdrawal from the EU took place on January 31, 2020. The EU and the United Kingdom reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the Agreement, which was applied provisionally beginning on January 1, 2021 and which entered into force on May 1, 2021. The Agreement focuses primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the EU and the United Kingdom will form two separate markets governed by two distinct regulatory and legal regimes. As such, the Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the United Kingdom is no longer part of the single market. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law the body of EU law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the EU. The MHRA may rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure until December 31, 2023.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the European Union's General Data Protection Regulation, or the GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area, or EEA, to the United Kingdom will remain lawful under the GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like a European Union member state in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a "third country" under the GDPR unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the United Kingdom. The United Kingdom has already determined that it considers all of the EU 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the EU/EEA remain unaffected.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. Additionally, in October 2022, the President signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Coverage, Pricing, and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any drug product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant

portion of the cost of such drug product candidates. Even if any drug product candidates we may develop are approved, sales of such drug product candidates will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers, and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such drug product candidates. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, drug product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover any drug product candidates we may develop could reduce physician utilization of such drug product candidates once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceuticals have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for any drug product candidates we may develop will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of any drug product candidates we may develop to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies (so called health technology assessments) in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving, or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious, or fraudulent or knowingly making, using, or causing to made or used a false record or statement to avoid, decrease, or conceal an obligation to pay money to the federal government;

- the federal civil monetary penalty and false statement laws and regulations relating to pricing and submission of pricing information for government programs, including penalties for knowingly and intentionally overcharging 340b eligible entities and the submission of false or fraudulent pricing information to government entities;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information;

- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

- the Foreign Corrupt Practices Act, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;

- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, or PPACA, as amended by the Health Care Education Reconciliation Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within HHS information related to payments and other transfers of value made by that entity to physicians, other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring pharmaceutical manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States. By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the PPACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. These Medicare sequester reductions were suspended and reduced through the end of June 2022 with the full 2% cut resuming thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our drug product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4%.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the TCJA, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

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

Pharmaceutical Price Initiatives

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

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act of 2022, or IRA, has been delayed by Congress to January 1, 2032.

On July 9, 2021, the President of the United States signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The Order directs HHS to create a plan within 45 days to combat "excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging." On September 9, 2021, HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments.

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

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug product candidates or additional pricing pressures.

Additional Regulations

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

Human Capital

As of December 31, 2022, we had 51 full-time employees and one part-time employee. Substantially all of our employees are in Boston, Massachusetts. None of our employees are represented by a labor union or covered by a collective bargaining agreement, and we believe our relationship with our employees is good. Additionally, we utilize independent contractors and other third parties to assist with various aspects of our drug and product development.

We recognize the value of our employees and are committed to being a workplace that encourages respect, collaboration, communication, transparency, and integrity. We seek to hire employees with diverse backgrounds and perspectives. Our success starts and ends with having the best talent, and as a result, we are focused on attracting, developing and retaining our employees. We offer employees a competitive and comprehensive benefits package. The principal purposes of our incentive plans are to attract, retain and motivate selected employees, consultants, advisors and directors through the granting of stock-based compensation awards and cash-based performance bonus awards, as applicable. We support employees attending industry conferences and obtaining professional licenses. We use a variety of human capital measures in managing our business, including: workforce demographics; inclusion and diversity; and employee health and safety.

We are committed to the health and safety of our employees. Beginning in March 2020, in response to the COVID-19 pandemic, we implemented additional safety protocols intended to help minimize the risk of virus transmission to our employees, including the establishment of remote working standards, pausing all non-essential travel worldwide for our employees, and limiting employee attendance at industry events and in-person work-related meetings along with measures designed to protect the health of all those entering our office.

Corporation Information

Our website address is www.cuebiopharma.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this Annual Report on Form 10-K or any other report or document we file with the Securities and Exchange Commission, or the SEC, and any reference to our website address is intended to be an inactive textual reference only.

Item 1A. Risk Factors

We are subject to various risks that may materially harm our business, prospects, financial condition and results of operations. This discussion highlights some of the risks that may affect future operating results. These are the risks and uncertainties we believe are most important for you to consider. We cannot be certain that we will successfully address these risks. If we are unable to address these risks, our business may not grow, our stock price may suffer, and we may be unable to stay in business. Additional risks and uncertainties not presently known to us, which we currently deem immaterial or which are similar to those faced by other companies in our industry or business in general, may also impair our business, prospects, results of operations and financial condition. The risks discussed below include forward-looking statements, and our actual results may differ substantially from those discussed in these forward-looking statements.

Risks Related to Our Business

We are a clinical-stage biopharmaceutical company, have no history of generating commercial revenue, have a history of operating losses, and may never achieve or maintain profitability.

We are a clinical-stage biopharmaceutical company. We have a limited operating history, have never generated revenue from product sales, and have a history of losses from operations. As of December 31, 2022, we had an accumulated deficit of approximately $250.5 million. Our ability to achieve commercial revenue-generating operations and, ultimately, achieve profitability will depend on whether we can obtain additional capital when we need it, complete the development of our technology, receive regulatory approval of our drug product candidates and find strategic collaborators that can incorporate our drug product candidates into new or existing drugs which can be successfully commercialized. There can be no assurance that we will ever generate commercial revenues or achieve profitability.

We currently do not have, and may never develop, any FDA-approved or commercialized products.

We currently do not have any products approved by the FDA or any other regulatory agency or any commercialized products and thus have never generated commercial revenue from product sales. We have not yet sought to obtain any regulatory approvals for any drug product candidates in the United States or in any foreign market. Therefore, any estimated timing for our drug product candidates to be commercialized would be highly speculative.

To date, we have invested substantial resources in an exclusive license with Einstein that forms the foundation for our drug product candidates and potential applications. For us to develop any products that might ultimately be commercialized, we will have to invest further time and capital in research and product development, regulatory compliance and market development. Therefore, we and our licensor, prospective business partners and other collaborators may never develop any products that can be commercialized. All of our development efforts will require substantial additional funding, none of which may result in any commercial revenue. Our efforts may not lead to commercially successful products for a number of reasons, including:

- we and our licensor, prospective business partners and other collaborators may not be able to complete research regarding, and nonclinical and clinical development of, our drug product candidates;
- regulatory approvals and marketing authorizations may not be achieved for our drug product candidates, or the scope of the approved indication may be narrower than sought;
- we and our licensor, prospective business partners and other collaborators may experience delays in our development program, clinical trials and the regulatory approval process;
- our technology may not prove to be safe and effective in clinical trials or preclinical studies and our drug product candidates may have adverse side effects which outweigh any potential benefit to patients;
- we may not be able to identify suitable collaborators to complete development or commercialization of our potential products;
- we may not be able to maintain, protect or expand our portfolio of intellectual property rights, including patents, trade secrets and know-how;

- any future products that are ultimately approved by the FDA or other regulatory bodies may not be commercially accepted in the marketplace by physicians or patients;

- any future products that are ultimately approved by the FDA or other regulatory bodies may not be able to be manufactured in commercial quantities or at an acceptable cost;

- physicians may not receive any reimbursement from third-party payors, or the level of reimbursement may be insufficient to support widespread adoption of any of our future products once approved by the FDA or other regulatory bodies; and

- rapid technological change may make our technology and drug product candidates obsolete.

Moreover, in the first quarter of 2022, we determined to prioritize and strategically focus on our CUE-101 and CUE-102 oncology programs in our CUE-100 series. We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs, as well as our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series, and there is no guarantee that we will be able to do so on favorable terms or at all.

We are substantially dependent on the success of our drug product candidates, only two of which are currently being tested in clinical trials, and significant additional research and development and clinical testing will be required before we can potentially seek regulatory approval for or commercialize any of our drug product candidates.

Our main focus and the investment of a significant portion of our efforts and financial resources has been in the development of our lead product candidate, CUE-101, for which we are currently actively conducting Phase 1 clinical trials and CUE-102, for which we are currently actively conducting a Phase 1 clinical trial. Our other drug product candidates are all at a preclinical stage. In the first quarter of 2022, we determined to prioritize and strategically focus on our CUE-101 and CUE-102 oncology programs in our CUE-100 series. We expect that additional trials of CUE-101 and CUE-102 will be required in order to gain approval by the FDA. Therefore, significant additional research and development activity and clinical testing are required before we and our collaborators will have a chance to achieve a commercially viable product from CUE-101, CUE-102 or our other drug product candidates. Our research and development efforts remain subject to all of the risks associated with the development of new biopharmaceutical products and treatments based on immune modulation. Development of the underlying technology may be affected by unanticipated technical or other problems, among other research and development issues, and the possible insufficiency of funds needed in order to complete development of these drug product candidates. Safety, regulatory and efficacy issues, clinical hurdles or other challenges may result in delays and cause us to incur additional expenses that would increase our losses. If we and our collaborators cannot complete, or if we experience significant delays in developing, our potential drug product candidates or products for use in potential commercial applications, particularly after incurring significant expenditures, our business may fail and investors may lose the entirety of their investment.

We have limited experience in conducting clinical trials and no history of commercializing biologic products, which may make it difficult to evaluate the prospects for our future viability.

Our operations to date have been limited to financing and staffing our company, conducting research and developing our core technologies, and identifying and optimizing our lead product clinical candidates. Additionally, we have conducted limited clinical testing of one of our drug product candidates. Although we have recruited a team that has experience with clinical trials in the United States, as a company, we have limited experience conducting clinical trials and have not had previous experience commercializing drug product candidates or submitting a BLA to the FDA or similar submissions to initiate clinical trials or obtain marketing authorization to foreign regulatory authorities. We cannot be certain that current clinical trials will begin or be completed on time, if at all, that our planned clinical trials will begin on time, if at all, or that our planned development programs would be acceptable to the FDA or other regulatory authorities, or that, if regulatory approval is obtained, our drug product candidates can be successfully commercialized. Clinical trials and commercializing our drug product candidates will require significant additional financial and management resources, and reliance on third-party clinical investigators, contract research organizations, or CROs, contract manufacturing organization, or CMOs, consultants and collaborators. Relying on third-party clinical investigators, CROs, CMOs or collaborators may result in delays that are outside of our control.

Furthermore, we may not have the financial resources to continue development of, or to enter into collaborations for, a product candidate if we experience any problems or other unforeseen events that delay or prevent regulatory approval of, or our ability to commercialize, drug product candidates, including:

- negative or inconclusive results from our IND-enabling studies, clinical trials or the clinical trials of other drug product candidates similar to ours, leading to a decision or requirement to conduct additional preclinical testing or clinical trials or abandon a program;
- delays in submitting INDs or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators to commence a clinical trial, or a suspension or termination of a clinical trial once commenced;
- conditions imposed by the FDA or a foreign regulatory authority regarding the number, scope or design of our clinical trials;
- delays in enrolling patients in clinical trials;
- high drop-out rates of patients;
- inadequate supply or quality of clinical trial materials or other supplies necessary to conduct our clinical trials;
- greater than anticipated clinical trial costs;
- poor effectiveness or unacceptable side effects of our drug product candidates during clinical trials;
- unfavorable FDA or other regulatory agency inspection and review of a clinical trial site;
- difficulty in establishing or managing relationships with CROs, CMOs, and clinical investigators;
- failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;
- serious and unexpected drug-related side effects or other safety issues experienced by participants in our clinical trials or by individuals using drugs similar to our drug product candidates;
- delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or
- varying interpretations of data by the FDA and foreign regulatory authorities.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For example, in December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans. Similarly, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted.

The COVID-19 pandemic has, and may continue to, adversely impact our business, including our clinical trials and preclinical studies.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. The COVID-19 pandemic, which began in 2020, has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures. Beginning in March 2020, in response to the COVID-19 pandemic, we implemented additional safety protocols intended to help minimize the risk of virus transmission to our employees, including the establishment of remote working standards, pausing all non-essential travel worldwide for our employees, and limiting employee attendance at industry events and in-person work-related meetings along with measures designed to protect the health of all those entering our office.

As a result of the COVID-19 pandemic, or other public health crises, we may in the future experience disruptions that could severely impact our business, clinical trials and preclinical studies, including:

- supply chain disruptions, making it difficult to order and receive materials needed for development of our drug product candidates;
- delays or disruptions in the manufacture of our drug product candidates by contract manufacturing organizations and vendors along their supply chain;
- government responses, including orders that make it difficult to remain open for business, and other seen and unforeseen actions taken by government agencies;
- absenteeism or loss of employees at our company, or at our collaborators, due to health reasons or government restrictions, that are needed to develop, validate, manufacture and perform other necessary functions for our operations;
- delays or difficulties in enrolling patients in our clinical trials;
- delays or disruptions in non-clinical experiments due to unforeseen circumstances at contract research organizations and vendors along their supply chain;
- increased rates of patients withdrawing from our clinical trials following enrollment as a result of contracting COVID-19 or other diseases, being forced to quarantine, or otherwise;
- interruption of key clinical trial activities due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures;
- interruption or delays in the operations of the FDA and comparable foreign regulatory agencies, which may impact approval timelines;
- equipment failures, loss of utilities and other disruptions that could impact our operations or render them inoperable; and
- effects of a local or global recession or depression that could harm the international banking system and limit our access to capital.

In January 2021, we were notified by our CMO that the manufacture of our GMP material for the CUE-102 drug product candidate would be delayed by approximately six weeks due to the invocation of the Defense Production Act, or DPA, which gives priority to the manufacture of vaccines and other drug products used to prevent or treat COVID-19. The GMP material for CUE-102 was ultimately manufactured in the second half of 2021. The delay in the manufacturing of our CUE-102 GMP batch impacted the expected filing date of the CUE-102 IND that was planned for the fourth quarter of 2021, which we filed on March 31, 2022. Despite our efforts to manage and remedy these impacts, their ultimate impact depends on factors beyond our knowledge or control, including the duration and severity of the pandemic, as well as third-party actions taken to contain its spread and mitigate its public health effects. Additionally, the anticipated economic consequences of the COVID-19 pandemic have adversely impacted financial markets, resulting in high share price volatility, reduced market liquidity, and substantial declines in the market prices of the securities of many publicly traded companies. Volatile or declining markets for equities could adversely affect our ability to raise capital when needed through the sale of shares of common stock or other equity or equity-linked securities. If these market conditions persist when we need to raise capital, and if we are unable to sell shares of our common stock under then prevailing market conditions, we might have to accept lower prices for our shares and

issue a larger number of shares than might have been the case under better market conditions, resulting in significant dilution of the interests of our stockholders.

On January 30, 2023, the current administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidances, including the clinical trial guidance and updates thereto. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates.

These and other factors arising from the COVID-19 pandemic or other public health crises could adversely impact our business generally, and could have a material adverse impact on our operations and financial condition and results.

Our current or planned clinical trials or those of our collaborators may reveal significant adverse events, toxicities or other side effects not seen in our preclinical studies and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our drug product candidates.

In order to obtain marketing approval for any of our biologic drug product candidates, we must demonstrate the safety, purity, and efficacy of the product candidate for the relevant clinical indication or indications through preclinical studies and clinical trials as well as additional supporting data. If our drug product candidates are associated with undesirable side effects in preclinical studies or clinical trials or have characteristics that are unexpected, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

We are conducting Phase 1 clinical trials for our lead product candidate, CUE-101, and a Phase 1 clinical trial for CUE-102, but otherwise we have not conducted any clinical trials. We have conducted various preclinical studies of our drug product candidates, but we do not know the predictive value of these studies for humans, and we cannot guarantee that any positive results in preclinical studies will successfully translate to human patients. It is not uncommon to observe results in human clinical trials that are unexpected based on preclinical testing, and many drug product candidates fail in clinical trials despite promising preclinical results. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their drug product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for their products. Human patients in clinical trials may suffer significant adverse events or other side effects not observed in our preclinical studies, including, but not limited to, immunogenic responses, organ toxicities such as liver, heart or kidney or other tolerability issues or possibly even death. The observed potency and kinetics of our drug product candidates in preclinical studies may not be observed in human clinical trials. If clinical trials of our drug product candidates fail to demonstrate efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our drug product candidates.

If significant adverse events or other side effects are observed in any of our future clinical trials, we may have difficulty recruiting patients to the clinical trial, patients may drop out of our trial, or we may be required to abandon the trial or our development efforts of that product candidate altogether. We, the FDA or other applicable regulatory authorities, or an Institutional Review Board may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage studies have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the drug from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. Any of these developments could materially harm our business, financial condition and prospects.

Further, if any of our drug product candidates obtains marketing approval, toxicities associated with our drug product candidates may also develop after such approval and lead to a requirement to conduct additional clinical safety trials, additional warnings being added to the labeling, significant restrictions on the use of the product or the withdrawal of the product from the market. We cannot predict whether our drug product candidates will cause toxicities in humans that would preclude or lead to the revocation of regulatory approval based on preclinical studies or clinical testing. However, any such event, were it to occur, would cause substantial harm to our business and financial condition and would result in the diversion of our management's attention.

Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

Results from preclinical studies or early clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our drug product candidates may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in preclinical studies or having successfully advanced through initial clinical trials or preliminary stages of clinical trials. There can be no assurance that the results seen in preclinical studies for any of our drug product candidates ultimately will result in success in clinical trials or that results seen in Phase 1 or 2 trials will be replicated in Phase 3 trials.

There is a high failure rate for drugs and biologic products proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy or requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

We plan to seek collaborations or strategic alliances. However, we may not be able to establish such relationships, and relationships we have established may not provide the expected benefits.

On November 14, 2017, we entered into the Merck Collaboration Agreement under which we collaborate with Merck in the development of specific Immuno-STATs targeting certain autoimmune diseases. Pursuant to the Merck Collaboration Agreement, Merck had acquired rights to develop, commercialize and sell specific Immuno-STATs relating to certain autoimmune disease and, in exchange for such rights, had agreed to make payments to us that include a licensing fee, milestone payments and sales royalties. The research term and financial support of research conducted under the Merck Collaboration Agreement expired on December 31, 2021, and as of December 20, 2022, the Merck Collaboration Agreement terminated.

Effective November 6, 2018, we entered into the LG Chem Agreement, for the development of our Immuno-STATs focused in the field of oncology. Pursuant to the LG Chem Agreement, we have granted certain exclusive license rights to LG Chem in Australia and in certain countries in Asia and LG Chem has agreed to provide certain services to us and to make payments to us that include licensing fees, milestone payments and sales royalties. This agreement does not commit LG Chem to a long-term relationship, and LG Chem may disengage with us at any time.

In the first quarter of 2022, we determined to prioritize and strategically focus on our CUE-101 and CUE-102 oncology programs in our CUE-100 series, and we are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs, as well as our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series, and there is no guarantee that we will be able to do so on favorable terms or at all.

We plan to also seek strategic alliances or collaborations with other third parties that we believe will complement or augment our development and commercialization efforts with respect to our drug product candidates and any future drug product candidates that we may develop. In addition, we currently do not have sales, marketing, manufacturing or distribution capabilities or arrangements. In order to commercialize our potential products, we plan to seek development and marketing partners or sublicensees to obtain necessary marketing, manufacturing and distribution capabilities.

Any of these relationships may require us to incur non-recurring and other charges, give up certain rights relating to our intellectual property and research and development activities, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, issue debt which may require liens on our assets and which will increase our monthly expense obligations, or disrupt our management and business. Moreover, we may not be successful in our efforts to establish additional strategic partnerships or other alternative arrangements for our drug product candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view our drug product candidates as having the requisite potential to demonstrate safety, purity, and efficacy. If we are unable to establish additional strategic partnerships or other alternative arrangements to develop our drug product candidates, the costs for us to independently develop our drug product candidates may be higher than we currently anticipate, which could materially harm our business prospects, financial condition and results of operation.

Further, collaborations involving our drug product candidates are subject to numerous risks, which may include the following:

- our collaborators may have significant discretion in determining the efforts and resources that they will apply to our collaboration as compared to their other then-existing collaborations;

- our collaborators may not pursue development and commercialization of our drug product candidates or may elect not to continue or renew development or commercialization of our programs based on clinical trial results, changes in their strategic focus due to the acquisition of competitive products, availability of funding or other external factors, such as a business combination that diverts resources or creates competing priorities;

- our collaborators may delay clinical trials, provide insufficient funding for a clinical trial, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;

- our collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our drug product candidates; a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of each of our potential products;

- our collaborators may not properly maintain or defend our intellectual property rights in accordance with the terms of our contractual arrangements with them or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to other potential liability;

- disputes may arise between us and a collaborator that cause the delay or termination of the research, development or commercialization of our drug product candidates, or that result in costly litigation or arbitration that diverts our managements' attention and our other resources;

- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable drug product candidates; and

- our collaborators may own or co-own intellectual property covering our potential products that results from our collaboration with them, and in such case, we would not have the exclusive right to commercialize such intellectual property without our collaborators' involvement and consent.

As a result, we may not be able to realize the benefit of collaboration agreements, strategic partnerships or licenses of our technology or potential products, which could delay our product development timelines or otherwise adversely affect our business. We also cannot be certain that, following a strategic transaction or license, we will achieve sufficient revenue or net income to justify such transaction. Any delays in entering into new collaborations or strategic partnership agreements related to our drug product candidates could delay the development and commercialization of our drug product candidates in certain geographies for certain indications, which would harm our business prospects, financial condition, and results of operations.

Our collaboration agreement with LG Chem contains exclusivity provisions that restrict our research and development activities.

We have granted to LG Chem under the LG Chem Agreement an exclusive license to develop, manufacture and commercialize CUE-101, as well as the Drug Product Candidates, in the LG Chem Territory. Under the LG Chem Agreement, we will engineer the selected Immuno-STAT for up to three alleles, which are expected to include the predominant alleles in the LG Chem Territory, while LG Chem will establish a CMC process for the development and commercialization of Drug Product Candidates.

These restrictions on our development, manufacturing, and commercialization activities could impact our ability to successfully develop certain drug product candidates, which could harm our future business prospects for commercializing drugs for those drug product candidates.

We may not be successful in our efforts to identify additional drug product candidates. Due to our limited resources and access to capital, we must prioritize development of certain drug product candidates; these decisions may prove to be wrong and may adversely affect our business.

In the first quarter of 2022, we decided to strategically focus on our CUE-101 and CUE-102 oncology programs in our CUE-100 series. We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series, and there is no guarantee that we will be able to do so on favorable terms or at all.

Although we may explore other therapeutic opportunities, in addition to the drug product candidates that we are currently developing, we may fail to identify successful drug product candidates for clinical development for a number of reasons. If we fail to identify additional potential drug product candidates, our business could be materially harmed.

Research programs to pursue the development of our drug product candidates for additional indications and to identify new drug product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. Our research programs may initially show promise in identifying potential indications and/or drug product candidates, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications and/or drug product candidates;
- our key platform technology, Immuno-STAT Biologics™, may not adequately enable us to design, discover and validate drug product candidates;
- potential drug product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs; or
- it may take greater human and financial resources than we will possess to identify additional therapeutic opportunities for our drug product candidates or to develop suitable potential drug product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our drug portfolio.

Because we have limited financial and human resources, we intend to initially focus on research programs and drug product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other drug product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our drug product candidates or to develop suitable potential drug product candidates through internal research programs, which could materially adversely affect our future growth and prospects. We may focus our efforts and resources on potential drug product candidates or other potential programs that ultimately prove to be unsuccessful.

We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results than our drug product candidates. Our competitors may include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources than we have, such as a larger research and development staff and experienced marketing and manufacturing organizations, established relationships with CROs and other collaborators, as well as established sales forces. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborative partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized or less costly than our drug product candidates or may develop proprietary technologies or secure patent protection and, in turn, exclude us from technologies that we may need for the development of our technologies and potential products.

Immunotherapy technologies are advancing at a rapid pace and we anticipate competing with companies developing bi-specific antibodies (e.g., Amgen, Immunocore and Roche Holding AG), cell therapies (e.g., Bristol-Myers Squibb, Gilead

Sciences and Novartis), antibody-drug conjugates (e.g., Gilead Sciences, Roche Holding AG, Seagen, Inc.), immune checkpoint inhibitors (e.g., Bristol-Myers Squibb, Merck and Pfizer), and targeted cytokines (e.g., Bristol Myers Squibb/Nektar, Neoleukin Therapeutics, Roche Holding AG and Sanofi) many of which have significantly greater financial and other resources than we currently have.

Even if we obtain regulatory approval of any of our drug product candidates, we may not be the first to market, and that may negatively affect the price or demand for our drug product candidates. Additionally, we may not be able to implement our business plan if the acceptance of our drug product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our drug product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our drug product candidates for use in limited circumstances. Furthermore, a competitor could obtain orphan product exclusivity from the FDA with respect to such competitor's product. If such competitor product is determined to be the same product as one of our drug product candidates, we may be prevented from obtaining approval from the FDA for such product candidate for the same indication for seven years, except in limited circumstances, and we may be subject to similar restrictions under non-U.S. regulations.

If we lose key management personnel, or if we fail to recruit additional highly skilled personnel, our ability to identify and develop new or next generation drug product candidates will be impaired, could result in loss of markets or market share and could make us less competitive.

We are highly dependent upon the principal members of our management team, including Daniel Passeri, M.Sc., our Chief Executive Officer, Anish Suri, our President and Chief Scientific Officer, Matteo Levisetti, our Chief Medical Officer, and other members of our scientific and clinical advisory team, including Steven Almo, Ph.D., the Chairman of our Scientific and Clinical Advisory Board. Our team has significant experience and knowledge of oncology drug discovery and development, T cell modulation, protein biochemistry and immunological assays, and the loss of any current or future team member could impair our ability to design, identify, and develop new intellectual property and drug product candidates and new scientific or product ideas. Additionally, if we lose the services of any of these persons, we would likely be forced to expend significant time and money in the pursuit of replacements, which may result in a delay in the development of our drug product candidates and the implementation of our business plan and plan of operations and diversion of our management's attention. We can give no assurance that we could find satisfactory replacements for our current and future key scientific and management employees on terms that would not be unduly expensive or burdensome to us.

To induce valuable personnel to remain at our company, in addition to salary and cash incentives, we have granted stock options and restricted stock units that vest over time. Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. Although we have employment agreements with our key employees, these employment agreements provide for at-will employment, which means that these employees could leave our employment at any time, for or without cause. We do not maintain "key man" insurance policies on the lives of these individuals or the lives of any of our other employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical and scientific personnel.

Our internal computer systems, or those used by third-party CROs, manufacturers or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs, manufacturers and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures, cyberattacks or cyber-intrusions, loss of funds or information from phishing or other fraudulent schemes, attachments to emails, persons inside our organization, or persons with access to systems inside our organization or those with whom we do business. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. Increased security threats and more sophisticated cybercrimes and cyberattacks pose a potential risk to the security and availability of our internal computer systems, networks and services, including those used by third-party CROs, manufacturers or other contractors or consultants, as well as the confidentiality, availability and integrity of our data and the data of potential trial participants or patients, employees and others. Although to our knowledge we have not experienced any such material system failure or security breach to date, if such an event were to occur, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information (such as individually identifiable health information), we could incur significant liabilities and the further development and commercialization of our drug product candidates could be delayed. In addition, the foreign, federal and state regulatory environment surrounding information security and privacy is

increasingly demanding, with frequent imposition of new and changing requirements. Compliance with changes in privacy and information security laws and standards may result in significant expense due to increased investment in technology and the development of new operational processes.

War, terrorism, other acts of violence, or natural or manmade disasters may affect the markets in which we operate, our patients and resources required in our research and development activities.

Our business may be adversely affected by political instability, disruption or destruction in a geographic region in which we operate, regardless of cause, including war, terrorism, riot, civil insurrection or social unrest, and natural or manmade disasters, including famine, flood, fire, earthquake, storm or pandemic events and spread of disease, such as the COVID-19 pandemic, and the significant military action against Ukraine by Russia. Such events may affect our business by increasing prices for resources required in our research and development activities or limiting our access to patients for our clinical trials which may delay our progress on one or more of our clinical or preclinical drug product candidates.

Risks Related to Our Reliance on Third Parties

We rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our drug product candidates and our business could be substantially harmed.

We rely upon and plan to continue to rely upon third-party CROs for execution of our clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs, including our CMO Catalent Pharma Solutions, LLC, or Catalent, are required to comply with FDA laws and regulations regarding current good clinical practice, or GCP, for all of our products in clinical development. Regulatory authorities enforce GCP through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCP, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot be certain that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under GMP regulations. While we work closely with our CMOs on the manufacturing process for our drug product candidates, including quality audits, we generally do not control the implementation of the manufacturing process of, and are completely dependent on, our CMOs for compliance with GMP regulatory requirements and for manufacture of both active drug substances and finished drug products. In addition, portions of the clinical trials for our drug product candidates may be conducted outside of the United States, which will make it more difficult for us to monitor CROs and perform visits of our clinical trial sites and will force us to rely heavily on CROs to ensure the proper and timely conduct of our clinical trials and compliance with applicable regulations, including GCP. Failure to comply with applicable regulations in the conduct of the clinical trials for our drug product candidates may require us to repeat clinical trials, which would delay the regulatory approval process.

Some of our CROs have an ability to terminate their respective agreements with us if, among other reasons, it can be reasonably demonstrated that the safety of the subjects participating in our clinical trials warrants such termination, if we make a general assignment for the benefit of our creditors or if we are liquidated. If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our preclinical and clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our drug product candidates. Consequently, our results of operations and the commercial prospects for our drug product candidates would be harmed, our costs could increase substantially and our ability to generate revenue could be delayed significantly.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We rely completely on third parties to manufacture our preclinical and clinical drug supplies for our drug product candidates.

We rely completely on third parties to manufacture clinical drug supplies for our drug product candidates. If we were to experience an unexpected loss of supply of our drug product candidates for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience disruptions in supply or delays, suspensions or terminations of clinical trials or regulatory submissions. We do not currently have nor do we plan to acquire the infrastructure or capability internally to manufacture our preclinical and clinical drug supplies and we lack the resources and the capability to manufacture any of our drug product candidates on a clinical or commercial scale. The facilities used by our contract manufacturers or other third-party manufacturers to manufacture our drug product candidates, including Catalent and Ajinomoto, must obtain and maintain approval by the FDA. While we work closely with our third-party manufacturers on the manufacturing process for our drug product candidates, including quality audits, we generally do not control the implementation of the manufacturing process of, and are completely dependent on, our contract manufacturers or other third-party manufacturers for compliance with GMP regulatory requirements and for manufacture of both active drug substances and finished drug products. If our contract manufacturers or other third-party manufacturers cannot successfully manufacture material that conforms to applicable specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities and we may not have sufficient access to supplies, which could significantly and adversely affect our operations.

In addition, we have no control over the ability of our contract manufacturers or other third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve, or withdraws approval for, these facilities for the manufacture of our products and drug product candidates, we may need to find alternative manufacturing facilities, which would significantly impact our ability to commercialize, develop, or obtain or maintain regulatory approval for our products and drug product candidates.

We also rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our drug product candidates for our clinical trials. There are a limited number of suppliers for raw materials that we use to manufacture our products and drug product candidates and we may need to assess alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our drug product candidates for our clinical trials. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these raw materials. Although we generally do not begin a clinical trial unless we believe we have a sufficient supply of a product candidate to complete the clinical trial, any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a contract manufacturer or other third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our drug product candidates.

Reliance on third-party manufacturers entails additional risks, including the possible breach of manufacturing agreements by the third party, the possible misappropriation of our proprietary information -- further discussed below under "*Risks Related to Intellectual Property and Other Legal Matters*" -- and the possible termination or non-renewal of an agreement by a third party at a time that is costly or inconvenient for us.

We expect to continue to depend on contract manufacturers or other third-party manufacturers for the foreseeable future. We may, however, be unable to enter into agreements or do so on commercially reasonable terms for potential future drug product candidates, which could have a material adverse impact upon our business.

We rely on certain sole or limited sources of supply for our drug product candidates and disruptions in the chain of supply have in the past, and may in the future, cause delays in developing, obtaining approval for, and commercializing our drug product candidates.

Currently, we use Catalent and Ajinomoto as our source of supply for manufacturing clinical supply of our lead product candidates, CUE-101 and CUE-102. If we experience multiple successive batch failures, or if supply from Catalent and Ajinomoto is otherwise interrupted, there could be a significant disruption in our product candidates supply. Any alternative vendor would need to be qualified through an IND supplement, which could result in delay of our clinical trials of CUE-101 and CUE-102.

The manufacturing processes for CUE-101 and CUE-102 and our other drug product candidates are complex, and it may difficult or impossible to finalize appropriate processes for the scaled manufacture of the drug product candidates. These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of any of our drug product candidates; cause us to incur higher costs; or prevent us from commercializing them successfully. Furthermore, if our suppliers fail to deliver the required clinical or commercial quantities of active pharmaceutical ingredient on a timely basis and at commercially reasonable prices and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed.

For example, in January 2021, we were notified by Catalent that the manufacture of our GMP material for the CUE-102 drug product candidate would be delayed by approximately six weeks due to the invocation of the DPA. The delay in the manufacturing of our CUE-102 GMP batch impacted the expected filing date of the CUE-102 IND that was planned for the fourth quarter of 2021 and which was filed on March 31, 2022.

Risks Related to Intellectual Property and Other Legal Matters

If we or our licensor is unable to protect our or its intellectual property, then our financial condition, results of operations and the value of our technology and potential products could be adversely affected.

Patents and other proprietary rights are essential to our business, and our ability to compete effectively is dependent upon the proprietary nature of our technologies. We also rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop, maintain and strengthen our competitive position. We seek to protect these, in part, through confidentiality agreements with certain employees, consultants and other parties. Our success will depend in part on the ability of ourselves and our licensor(s) to obtain, to maintain (including making periodic filings and payments) and to enforce patent protection for its intellectual property, particularly those patent applications and other intellectual property to which we have secured exclusive rights. We and our licensor(s) may not successfully prosecute or continue to prosecute the patent applications which we have licensed. Even if patents are issued in respect of pending patent applications, we or our licensor(s) may fail to maintain these patents, may determine not to pursue litigation against entities that are infringing upon these patents, or may pursue such enforcement less aggressively than we ordinarily would. Without adequate protection for the intellectual property that we own or license, others may be able to offer substantially identical products for sale, which could unfavorably affect our competitive business position and harm our business prospects. Even if issued, patents may be challenged, invalidated, or circumvented, which could limit our ability to stop competitors from marketing similar products or limit the length of the term of patent protection that we may have for our potential products.

Filing, prosecuting, maintaining and defending patents on drug product candidates in all countries throughout the world could be prohibitively expensive for us, and our intellectual property rights in some non-U.S. countries can have a different scope and strength than do those in the United States. In addition, the laws of certain non-U.S. countries do not protect intellectual property rights to the same extent as U.S. federal and state laws do. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing drugs made using our inventions in and into the United States or non-U.S. jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drugs and further, may export otherwise infringing drugs to non-U.S. jurisdictions where we have patent protection, but where enforcement rights are not as strong as those in the United States. These drugs may compete with our drug product candidates and our patent rights or other intellectual property rights may not be effective or adequate to prevent them from competing.

Many U.S.-based companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of some countries do not favor the enforcement of patents, trade secrets and other intellectual property, particularly those relating to biopharmaceutical products, which could make it difficult in those jurisdictions for us to stop the infringement or misappropriation of our patents or other intellectual property rights, or the marketing of competing drugs in violation of our proprietary rights. Proceedings to enforce our patent and other intellectual property rights in non-U.S. jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business.

Furthermore, such proceedings could put our patents at risk of being invalidated, held unenforceable or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims of infringement or misappropriation against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

If we are unable to protect the confidentiality of our proprietary information and know-how, the value of our technology and potential products could be adversely affected.

In addition to our licensed technology, we rely (and will continue to rely) upon, among other things, unpatented proprietary technology, processes, trade secrets, trademarks, and know-how. Any involuntary disclosure to or misappropriation by third parties of our confidential or proprietary information could enable competitors to duplicate or surpass our technological achievements, potentially eroding our competitive position in our market. We seek to protect confidential or proprietary information in part by confidentiality agreements with our employees, consultants and third parties. While we require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information and technology to enter into confidentiality agreements, we cannot be certain that this know-how, information and technology will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. These agreements may be terminated or breached, and we may not have adequate remedies for any such termination or breach. Furthermore, these agreements may not provide meaningful protection for our trade secrets and know-how in the event of unauthorized use or disclosure. To the extent that any of our staff was previously employed by other pharmaceutical, medical technology or biotechnology companies, those employers may allege violations of trade secrets and other similar claims in relation to their former employee's therapeutic development activities for us. Any dispute involving such employees may result in liabilities to us.

If we fail to comply with our obligations in the agreements under which we license development or commercialization rights to products or technology from third parties, we could lose license rights that are important to our business.

We hold an exclusive license from Einstein to intellectual property relating to identification of novel immunomodulators, novel epitopes, and novel immunotherapy drugs. This license imposes various developmental milestone obligations on us. If we fail to comply with any obligations under the license agreement and fail to cure such noncompliance, Einstein will have the right to terminate the agreement and our license. The existing patent applications or future patents to which we have rights based on our agreements with Einstein may be too specific and narrowly construed to prevent third parties from developing or designing around the protection provided by these patents. Additionally, we may lose our rights to the patents and patent applications we license in the event of termination of the license agreement. There is no assurance that we will be successful in meeting all of the milestones in the future on a timely basis or that this important license agreement will not be terminated for other reasons, depriving us of significant rights. The termination of this license agreement would have a material adverse effect on our financial condition, results of operations, and prospects.

If we are unable to patent and protect the intellectual property used in our potential products, others may be able to copy our innovations, which may impair our ability to compete effectively in our markets.

The strength of our anticipated patents will involve complex legal and scientific matters and can be uncertain. As described above under "Business - Our Intellectual Property," we own or license a number of pending patent applications. Our anticipated patents may be challenged or fail to result in issued patents and anticipated patents may be too specific and narrowly construed to prevent third parties from developing or designing around the protections provided by our intellectual property and in that event we may lose competitive advantage and our business may suffer. Further, the patent and patent applications that we license or have filed may fail to result in issued patents or the claims may need to be amended. Even after amendment, a patent may not issue. In that event, we may not obtain the exclusive use of the intellectual property that we seek, and we may lose competitive advantage, which could result in harm to our business.

Litigation or third-party claims of intellectual property infringement or challenges to the validity of our anticipated patents would require us to use resources to protect our technology and may prevent or delay our development, regulatory approval or commercialization of our drug product candidates.

If we are the target of claims by third parties asserting that our potential products or intellectual property infringe upon the rights of others, we may be forced to incur substantial expenses or divert substantial employee resources from our business.

If successful, those claims could result in our having to pay substantial damages or could prevent us from developing one or more drug product candidates. Further, if a patent infringement suit is brought against us or our collaborators, we or they could be forced to stop or delay research, development, manufacturing or sales of the product or product candidate that is the subject of the suit.

If we or our collaborators experience patent infringement claims, or if we elect to avoid potential claims others may be able to assert, we or our collaborators may choose to seek, or be required to seek, a license from the third party and would most likely be required to pay license fees or royalties or both. These licenses may not be available on acceptable terms, or at all. Even if we or our collaborators were able to obtain a license, the rights may be nonexclusive, which would give our competitors access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations if, as a result of actual or threatened patent infringement claims, we or our collaborators are unable to enter into license agreements on acceptable terms. This could harm our business significantly. The cost to us of any litigation or other proceeding, regardless of its merit, and even if resolved in our favor, could be substantial. Some of our competitors may be able to bear the costs of such litigation or proceedings more effectively than we can because of their having greater financial and human resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Intellectual property litigation and other proceedings may, regardless of their merit, also absorb significant management time and employee resources.

Although we are not currently aware of any litigation or other proceedings or third-party claims of intellectual property infringement, the therapeutic industry is characterized by many suits regarding patents and other intellectual property rights. Other parties may in the future allege that our activities infringe upon their patents or that we are employing their proprietary technology without authorization. We may not have identified all the patents, patent applications or published literature that affect our business either by blocking our ability to commercialize our potential products, by preventing the patentability of one or more aspects of our potential products or those of our licensor or by covering the same or similar technologies that may affect our ability to market our potential products. In addition, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our drug product candidates, and we have done so from time to time. We may fail to obtain future licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be unable to further develop and commercialize one or more of our drug product candidates, which could harm our business significantly.

Some intellectual property that we have in-licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as “march-in” rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

The majority of the intellectual property rights we have licensed are generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future drug product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as “march-in rights”). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

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

Patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the normal statutory term of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Further, normal statutory patent terms may be limited in the U.S. in the event there is a determination that the claims in different patents are directed to obvious variants of the same invention, which can negatively impact the normal statutory patent term. Even if patents covering our drug product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review of new drug product candidates, patents protecting such drug product candidates might expire before or shortly after such drug product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing drug product candidates similar or identical to ours.

Depending upon the timing, duration and conditions of any FDA marketing approval of our drug product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and similar legislation in the European Union. The Hatch-Waxman Amendments permit a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. However, we may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. Only one patent per approved product can be extended, the extension cannot extend the total patent term beyond 14 years from approval, and the scope of protection is not the full scope of the claims but is instead limited to the approved drug, a method for using it or a method for manufacturing it may be extended. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for the applicable product candidate will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case, and our competitive position, business, financial condition, results of operations, and prospects could be materially harmed.

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

We face an inherent risk of product liability as a result of the clinical testing of our drug product candidates and will face an even greater risk if we commercialize any drugs. For example, we may be sued if our drug product candidates cause or are perceived to cause injury or death or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the drug, negligence, strict liability or a breach of warranties. Claims could also be asserted under state or foreign consumer protection laws. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our drug product candidates. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our potential drugs;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management’s time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;

- loss of revenue;
- financial cost;
- exhaustion of any available insurance and our capital resources; and
- the inability to commercialize any product candidate.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of drugs we develop, alone or with collaborators. Our insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our insurance coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Risks Related to Government Regulation

We are subject to regulation in respect of our research and federal funding.

Because our licensor has conducted research under federal grants and we may conduct further research under federal grants, we will be subject to federal regulation in how we conduct our research and the agreement terms relating to those grants. There are also ethical guidelines promulgated by various governments and research institutions that we are required to follow in respect of our research. These guidelines are orientated towards research and experimentation involving humans and animals. Failure to follow the regulations, agreement terms and accepted scientific practices would jeopardize our grants and our results and the use of the results in further research and approval circumstances. Because our licensor has used federal funding, the government retains a "march-in" right in connection with these grants, which is the right to grant additional licenses to practice inventions developed from grant funding. The exercise of these "march-in" rights could result in decreased demand for our future products, which could have a material adverse effect on our results of operations and financial condition. In addition, any failure to comply with applicable laws or regulations could harm our business and divert our management's attention.

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming, and uncertain and may prevent us from obtaining approvals for the commercialization of any of our drug product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize, or will be delayed in commercializing, our drug product candidates, and our ability to generate revenue will be materially impaired.

Any of our drug product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any drug product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity, and potency. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any of our drug product candidates may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities, or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity, and novelty of the drug product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical, or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any of our drug product candidates, the commercial prospects for those drug product candidates may be harmed, and our ability to generate revenues will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent any of our drug product candidates from being marketed in such jurisdictions, which, in turn, would materially impair our ability to generate revenue.

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

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the withdrawal of the United Kingdom from the EU, commonly referred to as Brexit. The United Kingdom is no longer part of the European Single Market and European Union Customs Union. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to European Union rules under the Northern Ireland Protocol. The MHRA relies on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union. The MHRA may rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure until December 31, 2023. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm our business.

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

We may seek orphan drug designation for one or more of our drug product candidates, but even if such designation is granted, we may be unable to maintain any benefits associated with orphan drug designation, including market exclusivity that prevents the FDA or the EMA from approving other competing products.

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by the EMA in the European Union. Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the agency must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the United States. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition.

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

If approved, our product candidates that are licensed and regulated as biologics may face competition from biosimilars approved through an abbreviated regulatory pathway.

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, was enacted as part of the Patient Protection and Affordable Care Act, , as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, to establish an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as "interchangeable" based on its similarity to an approved biologic. Under the BPCIA, a reference biological product is granted 12 years of data exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product In addition, the licensure of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still develop and receive approval of a competing biologic, so long as its BLA does not reply on the reference product, sponsor's data or submit the application as a biosimilar application. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty, and any new policies or processes adopted by the FDA could have a material adverse effect on the future commercial prospects for our biological products.

We believe that any of the product candidates we develop as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider the subject product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of the reference products in a way that is similar to traditional generic substitution for non-biological products will depend on a number of marketplace and regulatory factors that are still

developing. Nonetheless, the approval of a biosimilar to our drug product candidates would have a material adverse impact on our business due to increased competition and pricing pressure.

We may seek fast-track designation or breakthrough therapy and priority review programs for our drug product candidates. Even if our drug product candidates receive one or more of these designations, the product candidate may not be subject to a faster review process nor does any such designation assure approval of our drug product candidates.

We aim to benefit from the FDA's fast track, breakthrough therapy and priority review programs. However, our drug product candidates may not receive an FDA fast-track designation, breakthrough therapy designation, or priority review. Without fast-track designation, submitting a BLA, and getting through the regulatory process to gain marketing approval is a lengthy process. Under fast-track designation, the FDA may initiate review of sections of a fast-track drug's BLA before the application is complete. However, the FDA's time period goal for reviewing an application does not begin until the last section of the BLA is submitted. On October 3, 2022, we received fast track designation for CUE-101 for the treatment of R/M HPV+ HNSCC as a monotherapy and in combination with KEYTRUDA.

The FDA has also established breakthrough therapy designation, which is for a product that is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner. We may seek breakthrough therapy designation for one or more of our drug product candidates, but there can be no assurance that we will receive such designation.

Under the FDA policies, a product candidate is eligible for priority review, or review within a six-month time frame from the time a complete BLA is accepted for filing, if the product candidate provides a significant improvement compared to marketed drugs in the treatment, diagnosis or prevention of a disease. A fast-track or breakthrough therapy designated drug product candidate would ordinarily meet the FDA's criteria for priority review.

The FDA has broad discretion with respect to whether or not to grant these designations to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, any such designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to licensure compared to conventional FDA procedures. As a result, while we may seek and receive these designations for our drug product candidates, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw these designations if it believes that the designation is no longer supported by data from our clinical development program. A delay in the review process or in the approval of our potential products will delay revenue from their potential sales and will increase the capital necessary to fund these product development programs.

We are also currently participating in Project Optimus, an initiative of the Oncology Center of Excellence at the FDA. This project focuses on dose optimization and dose selection in oncology drug development, and whether the current paradigm based on cytotoxic chemotherapeutics leads to doses and schedules of molecularly targeted therapies that provide more toxicity without additional efficacy, among other things. By participating in Project Optimus, we have the opportunity to meet with the FDA's Oncology Review Divisions early in our development programs, well before conducting trials intended for registration, to discuss dose-finding and dose optimization. The program thus allows us to develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials, with the objective of performing these studies as early as possible in the development program to bring promising new therapies to patients. There is no assurance, however, that our involvement in this program will lead to early discussions with the FDA or expedited studies leading to optimization of dose selection for our candidate products.

We may in the future, conduct clinical trials for certain of our product candidates at sites outside the United States. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the United States could subject us to additional delays and expense.

We may in the future conduct one or more of our clinical trials with trial sites that are located outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with good clinical practice. The FDA must be able to validate the data from the trial through an onsite inspection if necessary. The trial population must also have a similar profile to the U.S. population,

and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful, except to the extent the disease being studied does not typically occur in the United States. In addition, while these clinical trials are subject to the applicable local laws, the FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from clinical trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of our product candidates.

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

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

To obtain the necessary approval of our potential products, as a precondition, we will need to conduct various preclinical and clinical tests, all of which will be costly and time consuming, and may not provide results that will allow us to seek regulatory approval.

The number of preclinical and clinical tests that will be required for regulatory approval varies depending on the disease or condition to be treated, the method of treatment, the nature of the drug, the jurisdiction in which approval is sought and the applicable regulations. Regulatory agencies can delay, limit or deny approval of a product for many reasons. For example, regulatory agencies may:

- not deem a product candidate to be safe or effective;
- interpret data from preclinical and clinical testing differently than we do;
- not approve the manufacturing processes;
- conclude that our product candidate does not meet quality standards for durability, long-term reliability, biocompatibility, compatibility, or safety; and
- change their approval policies or adopt new regulations.

The FDA may make requests or suggestions regarding conduct of any clinical trials, resulting in an increased risk of difficulties or delays in obtaining regulatory approval in the United States. Foreign regulatory agencies may similarly have the ability to influence any clinical trials occurring outside the United States. Any of these occurrences could prove materially harmful to our operations and business.

Even if we, or any collaborators we may have, obtain marketing approvals for any of our drug product candidates, the terms of approvals and ongoing regulation of our products could require the substantial expenditure of resources and may limit how we, or they, manufacture and market our products, which could materially impair our ability to generate revenue.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, GMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product.

Accordingly, assuming we, or any collaborators we may have, receive marketing approval for one or more of our drug product candidates, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, and quality control. If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could have the marketing approvals for our products withdrawn by regulatory authorities and our, or such collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our business, operating results, financial condition, and prospects.

Any product candidate for which we obtain marketing approval could be subject to restrictions or withdrawal from the market, and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of products to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the Department of Justice. Violation of the Federal Food, Product, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a biologic product.

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

- restrictions on such products, manufacturers, or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on the distribution or use of a product;
- requirements to conduct post-marketing clinical trials;
- receipt of warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution, or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- suspension of any ongoing clinical trials;
- refusal to permit the import or export of our products;
- product seizure; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our drug product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any approval that we may have obtained and we may not achieve or sustain profitability. Further, any government investigation of alleged violations of law could require us to

expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any drug product candidates we develop and adversely affect our business, financial condition, results of operations, and prospects.

Similar restrictions apply to the approval of our products in the EU. The holder of a marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include: compliance with the EU's stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations; the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory; and the marketing and promotion of authorized drugs, which are strictly regulated in the EU and are also subject to EU Member State laws. The failure to comply with these and other EU requirements can also lead to significant penalties and sanctions.

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

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

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

Separately, in response to the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. As of early 2022, the FDA had resumed inspections of domestic and foreign facilities to ensure timely reviews of applications for medical products. However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required. Moreover, on January 30, 2023, the White House announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidance. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates. Regulatory authorities outside the United States have adopted or may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities.

Accordingly, if a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

Our relationships with healthcare providers, physicians, and third-party payors will be subject to applicable anti-kickback, fraud and abuse, and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits and future earnings.

Healthcare providers, physicians, and third-party payors play a primary role in the recommendation and prescription of any of our drug product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may

constrain the business or financial arrangements and relationships through which we market, sell, and distribute our products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving, or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;

- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid, or other government payors that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties;

- the federal Health Insurance Portability and Accountability Act of 1996, as further amended by the Health Information Technology for Economic and Clinical Health Act, which imposes certain requirements, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses, and health care providers;

- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services;

- the federal transparency requirements under the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report to the Department of Health and Human Services, or HHS, information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations; and

- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and certain state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

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

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products is prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

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

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

healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If commercial third-party payors or government payors fail to provide coverage or adequate reimbursement, our revenue and prospects for profitability would be harmed.

There is increasing pressure on biotechnology companies to reduce healthcare costs. In the United States, these pressures come from a variety of sources, such as managed care groups and institutional and government purchasers. Increased purchasing power of entities that negotiate on behalf of federal healthcare programs and private sector beneficiaries could increase pricing pressures in the future. Such pressures may also increase the risk of litigation or investigation by the government regarding pricing calculations. The biotechnology industry will likely face greater regulation and political and legal actions in the future.

There is increased uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within HHS, as CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement. Adverse pricing limitations may hinder our ability to recoup our investment in one or more future drug product candidates, even if our future drug product candidates obtain regulatory approval. Adverse pricing limitations prior to approval will also adversely affect us by reducing our commercial potential. Our ability to commercialize any potential products successfully also will depend in part on the extent to which reimbursement for these products and related treatments becomes available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers, pharmacy benefit managers, and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels.

A significant trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize in the future and, if reimbursement is available, what the level of reimbursement will be. Reimbursement may impact the demand for, or the price of, any product for which we obtain marketing approval in the future. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate that we successfully develop.

There may be significant delays in obtaining reimbursement for approved products, and coverage may be more limited than the purposes for which the product is approved by the FDA or regulatory authorities in other countries. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the product and the clinical setting in which it is used, may be based on payments allowed for lower cost products that are already reimbursed and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of products from countries where they may be sold at lower prices than in the United States. Our inability to promptly obtain coverage and profitable payment rates from both government funded and private payors for future products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize potential products and our overall financial condition.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our drug product candidates and affect the prices we may obtain for any products that are approved in the United States or foreign jurisdictions.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our drug product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any drug product candidates for which we obtain marketing approval. The pharmaceutical industry has been a particular focus of these efforts and have been significantly affected by legislative initiatives. Current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any FDA approved product.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

In March 2010, the PPACA was signed into law. In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 pursuant to the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. These Medicare sequester reductions were suspended and reduced through the end of June 2022 with the full 2% resuming thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our drug product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4%.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the "TCJA, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

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

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

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

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act of 2022, or IRA, has been delayed by Congress to January 1, 2032.

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

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or “catastrophic period” of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance

and co-payment costs, expanding eligibility for lower income subsidy plans, and placing price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

Accordingly, while it is currently unclear how the IRA will be effectuated, we cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug product candidates or additional pricing pressures.

In countries outside of the United States, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Compliance with the HIPAA security, privacy and breach notification regulations may increase our costs.

The HIPAA privacy, security and breach notification regulations, including the expanded requirements under HITECH, establish comprehensive federal standards with respect to the uses and disclosures of protected health information, or PHI, by health plans, healthcare providers and healthcare clearinghouses, in addition to setting standards to protect the confidentiality, integrity and security of PHI. The regulations establish a complex regulatory framework on a variety of subjects, including:

- the circumstances under which uses and disclosures of PHI are permitted or required without a specific authorization by the patient, including but not limited to treatment purposes, activities to obtain payments for our services, and our healthcare operations activities;
- a patient's rights to access, amend and receive an accounting of certain disclosures of PHI;
- requirements to notify individuals if there is a breach of their PHI;
- the contents of notices of privacy practices for PHI;
- administrative, technical and physical safeguards required of entities that use or receive PHI; and
- the protection of computing systems maintaining electronic PHI.

We have implemented practices intended to meet the requirements of the HIPAA privacy, security and breach notification regulations, as required by law. We are required to comply with federal privacy, security and breach notification regulations as well as varying state privacy, security and breach notification laws and regulations, which may be more stringent than federal HIPAA requirements. In addition, for healthcare data transfers from other countries relating to citizens of those countries, we must comply with the laws of those countries. The federal privacy regulations restrict our ability to use or disclose patient identifiable data, without patient authorization, for purposes other than payment, treatment, healthcare operations and certain other specified disclosures such as public health and governmental oversight of the healthcare industry.

HIPAA provides for significant fines and other penalties for wrongful use or disclosure of PHI, including potential civil and criminal fines and penalties. Computer networks are always vulnerable to breach and unauthorized persons may in the

future be able to exploit weaknesses in the security systems of our computer networks and gain access to PHI. Additionally, we share PHI with third-parties who are legally obligated to safeguard and maintain the confidentiality of PHI. Unauthorized persons may be able to gain access to PHI stored in such third-parties computer networks. Any wrongful use or disclosure of PHI by us or such third-parties, including disclosure due to data theft or unauthorized access to our or our third-parties computer networks, could subject us to fines or penalties that could adversely affect our business and results of operations. Although the HIPAA statute and regulations do not expressly provide for a private right of damages, we could also incur damages under state laws to private parties for the wrongful use or disclosure of confidential health information or other private personal information.

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

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the EU General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or €20 million, whichever is greater, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Similar actions are either in place or under way in the United States. There are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act—which went into effect on January 1, 2020—is creating similar risks and obligations as those created by GDPR, though the Act does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023, and significantly expanded the California Consumer Privacy Act to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut, already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future

legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with these requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

Our employees, principal investigators, consultants, and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

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

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

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

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

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

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the United States has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and drug product candidates outside of the United States, which could limit our growth potential and increase our development costs. The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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

Our business operations will subject us to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also may produce hazardous waste products. We expect to generally contract with third parties for the disposal of these materials and wastes. However, we cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. In addition, we may be required to incur substantial costs to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions and we may not have sufficient (or any) insurance to cover any such costs.

Risks Related to Owning Our Common Stock, Our Financial Results and Our Need for Financing

We anticipate future losses and negative cash flow, and it is uncertain if or when we will become profitable.

We do not expect to generate any commercial revenues until we successfully complete development of our first potential products and we are able to successfully commercialize them through sales and licensing, which we expect will take a number of years, if ever. We have not yet demonstrated our ability to generate commercial revenue, and we may never be able to produce commercial revenues or operate on a profitable basis. As a result, we have incurred losses since our inception and expect to experience operating losses and negative cash flow for the foreseeable future. Our drug product candidates may never be approved or become commercially viable. Even if we and our collaborators are able to commercialize our technology, which may include licensing, we may never recover our research and development expenses.

We will need substantial additional financing to support our growth and ongoing operations. Additional capital may be difficult to obtain, restrict our operations, require us to relinquish rights to our technologies or drug product candidates, encumber our assets and result in ongoing debt service cost, or result in additional dilution to our stockholders.

Our business will require additional capital for implementation of our long-term business plan and product development and commercialization. As we require additional funds, we may seek to fund our operations through the sale of additional equity securities, debt financing and/or strategic collaboration agreements. We cannot be sure that additional financing from any of these sources will be available when needed or that, if available, the additional financing will be obtained on favorable terms. Our ability to raise additional funds may be adversely impacted by general economic conditions, both inside and outside the U.S., including disruptions to, and instability and volatility in, the credit and financial markets in the U.S. and worldwide, heightened inflation, interest rate and currency rate fluctuations, and economic slowdown or recession as well as concerns related to the COVID-19 pandemic and geopolitical events, including civil or political unrest. In addition, market instability and volatility, high levels of inflation and interest rate fluctuations may increase our cost of financing or restrict our access to potential sources of future liquidity.

Our future funding requirements will depend on many factors, including, but not limited to:

- the progress, timing, scope and costs of our clinical trials, including the ability to timely enroll patients in our planned and potential future clinical trials;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable regulatory authorities, including the potential that the FDA or comparable regulatory authorities may require that we perform more studies than those that we currently expect;
- the number and characteristics of drug product candidates that we may in-license and develop;
- our ability to successfully commercialize our drug product candidates, if approved;
- the amount of sales and other revenues from drug product candidates that we may commercialize, if any, including the selling prices for such potential products and the availability of adequate third-party reimbursement;
- selling and marketing costs associated with our potential products, including the cost and timing of expanding our marketing and sales capabilities;
- the terms and timing of any potential future collaborations, licensing or other arrangements that we may establish;
- cash requirements of any future acquisitions and/or the development of other drug product candidates;
- the costs of operating as a public company;
- the cost and timing of completion of commercial-scale, outsourced manufacturing activities;
- the time and cost necessary to respond to technological and market developments;
- any disputes which may occur between us and Einstein, employees, collaborators or other prospective business partners; and
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

If we raise additional funds by selling shares of our common stock or other equity-linked securities, the ownership interest of our current stockholders will be diluted. We may seek to access the public or private capital markets whenever conditions are favorable, even if we do not have an immediate need for additional capital at that time. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or drug product candidates or to grant licenses on terms that may not be acceptable to us. If we raise additional funds through debt financing, we may have to grant a security interest on our assets to the future lenders, our debt service costs may be substantial, and the lenders may have a preferential position in connection with any future bankruptcy or liquidation involving the company. Our pledge of our assets as collateral to secure our obligations under our loan and security agreement, or the Loan Agreement, with Silicon Valley Bank, or SVB, may limit our ability to obtain additional debt financing. Under the Loan Agreement, we are also restricted from incurring future debt, granting liens, making investments, making acquisitions, distributing dividends on our common stock and selling assets and making certain other uses of our cash, without SVB's consent, subject in each case to certain exceptions.

If we are unable to raise additional capital when needed, we may be required to curtail the development of our technology or materially curtail or reduce our operations. We could be forced to sell or dispose of our rights or assets. Any inability to raise adequate funds on commercially reasonable terms could have a material adverse effect on our business, results of operation and financial condition, including the possibility that a lack of funds could cause our business to fail and the Company to dissolve and liquidate with little or no return to investors.

We hold a portion of our cash and cash equivalents that we use to meet our working capital and operating expense needs in deposit accounts, and our liquidity and operations could be adversely affected if a financial institution holding such funds fails.

We hold our a portion of cash and cash equivalents that we use to meet our working capital and operating expense needs in deposit accounts at multiple financial institutions. The balances held in these accounts typically exceed the Federal Deposit Insurance Corporation, or FDIC, standard deposit insurance limit of $250,000 per depositor and per institution. If a financial institution in which we hold such funds fails or is subject to significant adverse conditions in the financial or credit

markets, we could be subject to a risk of loss of all or a portion of such uninsured funds or be subject to a delay in accessing all or a portion of our funds. Any such loss or lack of access to these funds could adversely impact our short-term liquidity and ability to meet our operating expense obligations, including payroll obligations.

For example, on March 10, 2023, SVB was closed and the FDIC was appointed receiver for the bank. The FDIC created a successor bridge bank, and all deposits of SVB were transferred to the bridge bank under a systemic risk exception approved by the United States Department of the Treasury, the Federal Reserve and the FDIC. Access to and availability of deposits was delayed, though ultimately, in that case, restored. If financial institutions in which we may hold funds for working capital and operating expenses were to fail, we cannot provide any assurances that the applicable governmental agencies would take action to protect our uninsured deposits or make deposits available in a similar manner.

We also maintain investment accounts with financial institutions in which we hold our marketable securities and, if access to the funds we use for working capital and operating expenses is impaired, we may not be able to open new operating accounts or to sell investments or transfer funds from our investment accounts to new operating accounts in a timely manner sufficient to meet our operating expense obligations. In addition, to the extent that the financial institutions with which we hold securities fail or are associated with banks that fail, there may be delays or other access restrictions with respect to such securities, similar to those described above for deposit accounts.

We have a loan agreement that requires us to meet certain operating covenants and place restrictions on our operating and financial flexibility.

On February 15, 2022, we entered into the Loan Agreement, pursuant to which we have borrowed $10.0 million. The Loan Agreement is secured by substantially all of our properties, rights and assets, except for our intellectual property, which is subject to a negative pledge, and certain other customary exclusions. Because of the security interest, SVB's rights to repayment from a liquidation of the assets subject to that security interest would be senior to the rights of other creditors.

The Loan Agreement includes customary covenants including covenants requiring us to maintain our corporate existence and governmental approvals, deliver certain financial reports and maintain insurance coverage as well as a requirement that we maintain in our accounts at SVB unrestricted and unencumbered cash equal to the lesser of all of our cash and 110% of our obligations to SVB. Additionally, we are restricted in our ability to transfer collateral, incur additional indebtedness, engage in mergers or acquisitions, pay dividends or make other distributions, make investments, create liens, sell assets and agree to a change in control. Upon the occurrence of an event of default, which includes our failure to satisfy our payment obligations under the Loan Agreement, the breach of certain of these covenants under the Loan Agreement, or the occurrence of a material adverse change in our business, SVB is entitled to accelerate amounts due under the Loan Agreement and dispose the collateral as permitted under applicable law. Any declaration by SVB of an event of default could significantly harm our business and prospects and could cause the price of our common stock to decline.

On March 10, 2023, SVB was closed and the FDIC was appointed receiver for the bank. The FDIC created a successor bridge bank, Silicon Valley Bridge Bank, N.A., or SVBB, and all deposits of SVB were transferred to SVBB under a systemic risk exception approved by the United States Department of the Treasury, the Federal Reserve and the FDIC. SVBB continues to hold our Term Loans under the same existing terms and covenants which were in place with SVB. We are working with SVBB to seek more flexibility under the Loan Agreement in respect of requirements for how our accounts are held.

We are a "smaller reporting company," and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are a smaller reporting company, and we will remain a smaller reporting company until the fiscal year following the determination that our voting and non-voting common shares held by non-affiliates is more than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are less than $100 million during the most recently completed fiscal year and our voting and non-voting common shares held by non-affiliates is more than $700 million measured on the last business day of our second fiscal quarter. Smaller reporting companies have reduced disclosure obligations, such as an exemption from providing selected financial data and an ability to provide simplified executive compensation information and only two years of audited financial statements.

We have elected to take advantage of certain of the reduced reporting obligations. Investors may find our common stock less attractive as a result of our reliance on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Our stock price can be volatile and investors may have difficulty selling their shares.

Our common stock is currently listed on the Nasdaq Capital Market under the symbol "CUE." The price of our common stock may fluctuate significantly in response to market and other factors, some of which are beyond our control, including those listed in this "Item 1A. Risk Factors" section and other, unknown factors. Our stock price may also be affected by:

- setbacks with respect to our research and development programs;
- announcements of therapeutic innovations or new products by us or our competitors;
- adverse actions taken by regulatory agencies with respect to our clinical trials;
- any adverse changes to our relationship with collaborators;
- results of internal and external studies and clinical trials;
- result of our business development efforts;
- variations in the level of expenses related to our existing drug product candidates or preclinical and clinical development programs;
- any intellectual property infringement actions in which we may become involved;
- variations in our results of operations;
- press reports, whether or not true, about our business;
- additions to or departures of our management;
- release or expiry of lock-up or other transfer restrictions on our common stock;
- sales or perceived potential sales of additional shares of our common stock;
- sales of our common stock by us, our executive officers and directors or our stockholders in the future; and
- general economic and market conditions and overall fluctuations in the U.S. equity markets.

Any of these factors may result in large and sudden changes in the volume and trading price of our common stock. In addition, the stock market, in general, and small pharmaceutical and biotechnology companies have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors beyond our control may negatively affect the market price of our common stock, regardless of our actual operating performance, and cause the price of our common stock to decline rapidly and unexpectedly.

We may be subject to securities litigation, which is expensive and could divert management attention.

The price of our common stock can be volatile, and in the past companies that have experienced volatility in the market price of their common stock have been subject to an increased incidence of securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

If securities or industry analysts do not publish research reports about our business, or if they issue an adverse opinion about our business, the price of our securities and trading volume could decline.

The trading market for our securities is influenced by the research and reports that industry or securities analysts publish about us or our business. There can be no assurance that existing analysts will continue to cover us or that new analysts will begin to cover us. There is also no assurance that any covering analyst will provide favorable coverage. Although we have obtained analyst coverage, if one or more of the analysts who cover us issues an adverse opinion about our company, the price of our securities would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause the price of our securities or trading volume to decline.

We have not paid dividends in the past and have no immediate plans to pay dividends.

We plan to reinvest all of our earnings, to the extent we have earnings, in order to further develop our technology and potential products and to cover operating costs. We do not plan to pay any cash dividends with respect to our securities in the foreseeable future. We cannot assure you that we would, at any time, generate sufficient surplus cash that would be available for distribution to the holders of our common stock as a dividend. In addition, our ability to pay cash dividends is currently restricted by the terms of the Loan Agreement, and future debt financing arrangements may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock.

Our ability to use net operating loss carryforwards and research tax credits to reduce future tax payments may be limited or restricted.

We have generated significant net operating loss carryforwards, or NOLs, and research and development tax credits, or R&D credits, as a result of our incurrence of losses and our conduct of research activities since inception. We generally are able to carry NOLs and R&D credits forward to reduce our tax liability in future years. However, our ability to utilize the NOLs and R&D credits is subject to the rules of Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, respectively. Those sections generally restrict the use of NOLs and R&D credits after an "ownership change." An ownership change occurs if, among other things, the stockholders (or specified groups of stockholders) who own or have owned, directly or indirectly, 5% or more of a corporation's common stock or are otherwise treated as 5% stockholders under Section 382 of the code and the United States Treasury Department regulations promulgated thereunder increase their aggregate percentage ownership of that corporation's stock by more than 50 percentage points over the lowest percentage of the stock owned by these stockholders over the applicable testing period. In the event of an ownership change, Section 382 imposes an annual limitation on the amount of taxable income a corporation may offset with NOL carry forwards and Section 383 imposes an annual limitation on the amount of tax a corporation may offset with business credit (including the R&D credit) carry forwards.

We may have experienced an "ownership change" within the meaning of Section 382 in the past and there can be no assurance that we will not experience additional ownership changes in the future. As a result, our NOLs and business credits (including the R&D credit) may be subject to limitations and we may be required to pay taxes earlier and in larger amounts than would be the case if our NOLs or R&D credits were freely usable.

We incur significant costs as a result of being a public company and our management is required to devote substantial time to meet compliance obligations.

As a public company, and particularly as we are no longer an emerging growth company, we incur significant legal, accounting and other expenses. We are subject to reporting requirements of the Exchange Act and the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC that impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. In addition, there are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Wall Street Reform and Protection Act that increase public companies' legal and financial compliance costs, make some activities more difficult, time-consuming or costly and may also place undue strain on personnel, systems and resources. Our management and other personnel devote a substantial amount of time to these compliance initiatives. In addition, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers.

Our charter documents and Delaware law may inhibit a takeover that stockholders consider favorable.

Provisions of our amended and restated certificate of incorporation, or the Certificate of Incorporation, and our amended and restated bylaws, or the Bylaws, and applicable provisions of Delaware law may delay or discourage transactions involving an actual or potential change in control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. The provisions in our Certificate of Incorporation and Bylaws:

- authorize our board of directors to issue preferred stock without stockholder approval and to designate the rights, preferences and privileges of each class; if issued, such preferred stock would increase the number of outstanding shares of our common stock and could include terms that may deter an acquisition of us;

- limit who may call stockholder meetings;

- do not provide for cumulative voting rights;

- provide that all vacancies may be filled only by the affirmative vote of a majority of directors then in office, even if less than a quorum;

- provide that stockholders must comply with advance notice procedures with respect to stockholder proposals and the nomination of candidates for director;

- provide that stockholders may only amend our Certificate of Incorporation and Bylaws upon a supermajority vote of stockholders; and

- provide that the Court of Chancery of the State of Delaware will be the exclusive forum for certain legal claims.

In addition, Section 203 of the Delaware General Corporation Law may limit our ability to engage in any business combination with a person who beneficially owns 15% or more of our outstanding voting stock unless certain conditions are satisfied. This restriction lasts for a period of three years following the share acquisition. These provisions may have the effect of entrenching our management team and may deprive you of the opportunity to sell your shares to potential acquirers at a premium over prevailing prices. This potential inability to obtain a control premium could reduce the price of our common stock.

Our Certificate of Incorporation provides, subject to certain exceptions, that the Court of Chancery of the State of Delaware will be the sole and exclusive forum for certain stockholder litigation matters, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or stockholders.

Our Certificate of Incorporation provides, subject to limited exceptions, that the Court of Chancery of the State of Delaware will, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders; (3) any action asserting a claim against us, any director or our officers and employees arising pursuant to any provision of the Delaware General Corporation Law, our Certificate of Incorporation or our Bylaws, or as to which the Delaware General Corporation Law confers exclusive jurisdiction on the Court of Chancery; or (4) any action asserting a claim against us, any director or our officers or employees that is governed by the internal affairs doctrine. The choice of forum provisions will not apply to claims arising under the Securities Act, the Exchange Act, or any other claim for which federal courts have exclusive jurisdiction. Any person or entity purchasing or otherwise acquiring any interest in shares of our common stock shall be deemed to have notice of and to have consented to the provisions of our Certificate of Incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, other employees or stockholders which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provision that will be contained in our Certificate of Incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could materially adversely affect our business, financial condition and results of operations.

If we are unable to implement and maintain effective internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our securities may decrease.

As a public company, we are required to maintain internal control over financial reporting and to report any material weaknesses in such internal controls. Section 404 of the Sarbanes-Oxley Act requires that we evaluate and determine the effectiveness of our internal control over financial reporting and provide a management report on our internal control over financial reporting. Until such time as we are no longer a "smaller reporting company" with less than $100 million in annual revenue, our auditors will not be required to attest as to our internal control over financial reporting.

If we are unable to comply with the requirements of Section 404 in a timely manner, if we are unable to assert that our internal control over financial reporting is effective or, once required, provide an attestation report from our independent

registered public accounting firm, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our common stock could decrease. We could also become subject to stockholder or other third-party litigation as well as investigations by the stock exchange on which our securities are listed, the SEC or other regulatory authorities, which could require additional financial and management resources and could result in fines, trading suspensions or other remedies.

A significant number of our total outstanding shares may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is performing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Our outstanding shares of common stock may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended, or the Securities Act, or to the extent such shares have already been registered under the Securities Act and are held by non-affiliates of ours.

In November 2022, we completed a private placement of shares of our common stock, pre-funded warrants to purchase shares of our common stock and warrants to purchase shares of our common stock (or pre-funded warrants to purchase common stock in lieu thereof) to several accredited investors. We have filed a registration statement covering the resale of these shares by the purchasers in this private placement, and have agreed to keep such registration statements effective until the date the shares covered by the registration statement have been sold or can be resold without restriction under Rule 144 of the Securities Act.

In addition, we have filed registration statements registering all shares of common stock that we may issue under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to black-out periods and volume limitations applicable to affiliates.

We currently have on file with the SEC a universal shelf registration statement which allows us to offer and sell registered common stock, preferred stock, debt securities, warrants, rights and/or units from time to time pursuant to one or more offerings at prices and terms to be determined at the time of sale.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our principal office is located in Boston, Massachusetts. In March 2022, we entered into a License Agreement pursuant to which we relocated our corporate headquarters from Cambridge, Massachusetts to Boston, Massachusetts. We currently lease approximately 13,000 square feet of office and laboratory space under a lease that expires in April 2026. We use this space as our principal executive offices and for general office, research and development, and laboratory uses. The monthly rental rate is currently $209,700 until April 2023 and when it will increase to $218,088. In April 2024, it will increase to $226,800 and in April 2025 will increase to $235,883 for the remainder of the term through April 2026. We also lease additional laboratory space consisting of one procedure and two holding rooms. The monthly payments due under this lease agreement will be approximately $59,000 until November 2023 and will increase to $61,500 for the remainder of the lease term which expires in November 2024.

Item 3. Legal Proceedings

We are not currently a party to any pending legal proceedings that we believe will have a material adverse effect on our business or financial conditions. We may, however, be subject to various claims and legal actions arising in the ordinary course of business from time to time.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Common Stock

Our shares of common stock have been listed on the Nasdaq Capital Market under the symbol "CUE" since January 2, 2018. Prior to that date, there was no public trading market for our common stock.

As of March 13, 2023, there were approximately 108 registered holders of our common stock.

Dividend Policy

We have never paid cash dividends on our securities and we do not anticipate paying any cash dividends on our shares of common stock in the foreseeable future. In addition, our ability to pay cash dividends is currently restricted by the terms of the Loan Agreement, and future debt financing arrangements may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. We intend to retain any future earnings for reinvestment in our business. Any future determination to pay cash dividends will be at the discretion of our board of directors, and will be dependent upon our financial condition, results of operations, capital requirements and such other factors as our board of directors deems relevant.

Recent Sales of Unregistered Securities

During the period covered by this Annual Report on Form 10-K, we did not issue any unregistered equity securities other than pursuant to transactions previously disclosed in our Current Reports on Form 8-K.

Item 6. [Reserved]

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

The following discussion of our financial condition and results of operations should be read in conjunction with the financial statements and the related notes thereto included elsewhere in this Annual Report on Form 10-K.

Overview

We are a clinical-stage biopharmaceutical company engineering a novel class of injectable biologics to selectively engage and modulate targeted T cells directly within the patient's body. We believe our proprietary Immuno-STAT™ (*Selective Targeting and Alteration of T Cells*) platform, as described below, will allow us to harness the potential of the patient's intrinsic immune repertoire to fully exploit its potential to fight cancer and restore health while avoiding the deleterious side effects of broad immune activation. In addition to the highly selective modulation of T cell activity, we believe the core features of Immuno-STATs offer competitive differentiation, including modularity, manufacturability, and convenient administration that allows for versatility to treat a broad range of disease.

While we have demonstrated the potential application of our protein designed Immuno-STAT platform in preclinical studies in cancer, chronic infectious disease, and autoimmune disease, we are currently prioritizing and strategically focusing on CUE-101 and CUE-102 drug product candidates for treating cancer in our CUE-100 series, which exploits rationally engineered interleukin 2, or IL-2, in context of the core Immuno-STAT framework for selective activation of targeted tumor-specific T cells. We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series.

Our drug product candidates are in various stages of clinical and preclinical development, and while we believe that these candidates hold significant potential value, our activities are also subject to significant risks and uncertainties. We have not yet commenced any commercial revenue-generating operations, have limited cash flows from operations, and will need to access additional capital to fund our growth and ongoing business operations.

The COVID-19 Pandemic

The COVID-19 pandemic prompted governments and regulatory bodies throughout the world to enact restrictions on businesses, public gatherings and travel to minimize the risk of virus transmission in the population. Beginning in March 2020, we undertook precautionary measures intended to help mitigate the risk of virus transmission to our employees, including the establishment of remote working standards, pausing all non-essential travel worldwide for our employees, and limiting employee attendance at industry events and in-person work-related meetings, along with measures designed to protect the health of all those entering our office.

We have experienced supply chain disruptions for lab supplies used in our preclinical research as well as delays with some of our CROs. In January 2021, we were notified by our contract manufacturing organization, or CMO, that the manufacture of our good manufacturing practice, or GMP, material for the CUE-102 drug product candidate would be delayed by approximately six weeks due to the invocation of the Defense Production Act, or DPA, which gives priority to the manufacture of vaccines and other drug products used to prevent or treat COVID-19. The delay in the manufacturing of our CUE-102 GMP batch impacted the filing date of the CUE-102 IND, which was planned for the fourth quarter of 2021 but was instead filed on March 31, 2022.

Plan of Operation

Our technology is in the development phase. We believe that our platforms have the potential for creating a diverse pipeline of promising drug product candidates addressing multiple medical indications. We intend to maximize the value and probability of commercialization of our Immuno-STAT drug product candidates by focusing on researching, testing, optimizing, conducting pilot studies, performing early-stage clinical development and potentially partnering, where appropriate, for more extensive, later stages of clinical development, as well as seeking extensive patent protection and intellectual property development.

Since we are a development-stage company, the majority of our business activities to date and our planned future activities will be devoted to furthering research and development.

A fundamental part of our corporate development strategy is to establish one or more strategic partnerships with leading pharmaceutical or biotechnology organizations that will allow us to more fully exploit the potential of our technology platform, such as our collaboration described below under the heading "Collaboration Agreement with LG Chem".

Critical Accounting Estimates and Significant Judgments

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States, or U.S. GAAP. The preparation of our financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of our financial statements, and the reported revenue and expenses during the reported periods. We evaluate these estimates and judgments, including those described below, on an ongoing basis. We base our estimates on historical experience, known trends and events, contractual milestones and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While the Company's significant accounting policies are more fully described in Note 2 to our consolidated financial statements appearing elsewhere in this Form 10-K, we believe that the estimates, assumptions and judgments involved in the following accounting policies may have the greatest potential impact on the financial statements, so we consider these to be our critical accounting policies and estimates. There were no material changes to our critical accounting policies and estimates during the year ended December 31, 2022.

Revenue Recognition

We recognize collaboration revenue under certain of our license and collaboration agreements that are within the scope of Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers, or* ASC 606. Our contracts with customers typically include promises related to licenses to intellectual property and research and development services. If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from non-refundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. Accordingly, the transaction price is generally comprised of a fixed fee due at contract inception and variable consideration in the form of milestone payments due upon the achievement of specified events and tiered royalties earned when customers recognize net sales of licensed products. We measure the transaction price based on the amount of consideration to which we expect to be entitled in exchange for transferring the promised goods and/or services to the customer. We utilize the "most likely amount" method to estimate the amount of variable consideration, to predict the amount of consideration to which we will be entitled for our one open contract. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved. At the inception of each arrangement that includes development and regulatory milestone payments, we evaluate whether the associated event is considered probable of achievement and estimates the amount to be included in the transaction price using the most likely amount method.

Research and Development Costs

Research and development expenses consist primarily of compensation costs, fees paid to consultants, outside service providers and organizations (including research institutes at universities), facility costs, and development and clinical trial costs with respect to our drug product candidates.

Research and development expenses incurred under contracts are expensed ratably over the life of the underlying contracts, unless the achievement of milestones, the completion of contracted work, or other information indicates that a different pattern of performance is more appropriate. Other research and development expenses are charged to operations as incurred.

Nonrefundable advance payments are recognized as an expense as the related services are performed. We evaluate whether we expect the services to be rendered at each quarter end and year end reporting date. If we do not expect the services to be rendered, the advance payment is charged to expense. Nonrefundable advance payments for research and development services are included in prepaid and other current assets on the balance sheet. To the extent that a nonrefundable advance

payment is for contracted services to be performed within 12 months from the reporting date, such advance is included in current assets; otherwise, such advance is included in non-current assets.

We evaluate the status of our research and development agreements and contracts, and the carrying amount of the related assets and liabilities, at each quarter end and year end reporting date, and adjust the carrying amounts and their classification on the balance sheet as appropriate.

Stock-Based Compensation

We periodically issue stock-based awards to officers, directors, employees, Scientific and Clinical Advisory Board members, and consultants for services rendered. Such issuances vest and expire according to terms established at the issuance date.

Stock-based payments to officers, directors, employees, Scientific and Clinical Advisory Board members and consultants, including grants of employee stock options, are recognized in the financial statements based on their grant date fair values. Stock option grants, which are generally time-vested, are measured at the grant date fair value and charged to operations on a straight-line basis over the service period, which generally approximates the vesting term. We also grant performance-based awards periodically to our officers. We recognize compensation costs related to performance awards over the requisite service period if and when we conclude that it is probable that the performance condition will be achieved.

The fair value of stock options and restricted stock units is determined utilizing the Black-Scholes option-pricing model, which is affected by several variables, including the risk-free interest rate, the expected dividend yield, the life of the equity award, the exercise price of the stock option as compared to the fair value of the common stock on the grant date, and the estimated volatility of the common stock over the term of the equity award.

The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant. Until we have established a trading history for our common stock that approximates the expected term of the options, estimated volatility is based on the average historical volatilities of comparable public companies in a similar industry. The expected dividend yield is based on the current yield at the grant date; we have never declared or paid dividends and have no plans to do so for the foreseeable future. As permitted by Staff Accounting Bulletin No. 107, due to our limited trading history and option activity, management utilizes the simplified method to estimate the expected term of options at the date of grant. The exercise price is determined based on the fair value of our common stock at the date of grant. We account for forfeitures as they occur.

We recognize the fair value of stock-based compensation in general and administrative expenses and in research and development expenses in the consolidated statements of operations and comprehensive loss, depending on the type of services provided by the recipient of the equity award.

Income Taxes

We account for income taxes under an asset and liability approach for financial accounting and reporting for income taxes. Accordingly, we recognize deferred tax assets and liabilities for the expected impact of differences between the financial statements and the tax basis of assets and liabilities.

We account for uncertainties in income tax law under a comprehensive model for the financial statement recognition, measurement, presentation and disclosure of uncertain tax positions taken or expected to be taken in income tax returns as prescribed by GAAP. The tax effects of a position are recognized only if it is “more-likely-than-not” to be sustained by the taxing authority as of the reporting date. If the tax position is not considered “more-likely-than-not” to be sustained, then no benefits of the position are recognized.

We record a valuation allowance to reduce our deferred tax assets to the amount that is more likely than not to be realized. In the event we were to determine that we would be able to realize our deferred tax assets in the future in excess of its recorded amount, an adjustment to the deferred tax assets would be credited to operations in the period such determination was made. Likewise, should we determine that we would not be able to realize all or part of our deferred tax assets in the future, an adjustment to the deferred tax assets would be charged to operations in the period such determination was made.

We are subject to U.S. federal and Massachusetts state income taxes. As our net operating losses have yet to be utilized, all previous tax years remain open to examination by federal and state taxing authorities in which we currently operate.

We recognize interest accrued relative to unrecognized tax benefits in interest expense and penalties in operating expense.

Recent Accounting Pronouncements and Adopted Standards

A discussion of recent accounting pronouncements is included in Note 2 to the consolidated financial statements in this Annual Report on Form 10-K.

Significant Contracts and Agreements Related to Research and Development Activities

Einstein License Agreement

On January 14, 2015, we entered into a license agreement, as amended and restated on July 31, 2017, and as amended on October 30, 2018, or the Einstein License, with Albert Einstein College of Medicine, or Einstein, for certain patent rights relating to our core technology platform for the engineering of biologics to control T cell activity, precision, immune-modulatory drug product candidates, and two supporting technologies that enable the discovery of costimulatory signaling molecules (ligands) and T cell targeting peptides.

We hold an exclusive worldwide license, with the right to sublicense, import, make, have made, use, provide, offer to sell, and sell all products, processes and services that use the patents covered by the Einstein License, including certain technology received from Einstein related thereto, or the Licensed Products. Under the Einstein License, we are required to:

- Pay royalties and amounts based on certain percentage of proceeds, as defined in the Einstein License, from sales of Licensed Products and sublicense agreements.
- Pay escalating annual maintenance fees, which are non-refundable, but are creditable against the amount due to Einstein for royalties.
- Make significant payments based upon the achievement of certain milestones, as defined in the Einstein License. At December 31, 2022, two of these milestones had been achieved, as we had filed an investigational new drug application, or IND, in 2019, and initiated the investigator sponsored Phase 1b neoadjuvant clinical trial for CUE-101 in 2021.
- Incur minimum product development costs per year until the first commercial sale of the first Licensed Product.

We were in compliance with our obligations under the Einstein License at December 31, 2022 and 2021.

The Einstein License expires upon the expiration of the last obligation to make royalty payments to Einstein which may be due with respect to certain Licensed Products, unless terminated earlier under the provisions thereof. The Einstein License includes certain termination provisions that will be triggered if we fail to meet our obligations thereunder.

We account for the costs incurred in connection with the Einstein License in accordance with ASC 730, *Research and Development*. For the years ended December 31, 2022 and 2021, costs incurred with respect to the Einstein License aggregated $0 and $619,000, respectively. Such costs are included in research and development costs in our consolidated statements of operations and other comprehensive loss.

Pursuant to the Einstein License, we issued to Einstein 671,572 shares of our common stock in connection with the consummation of the initial public offering of our common stock on December 27, 2017.

See “Our License Agreement with Einstein” under Part I, Item 1 of the Annual Report on Form 10-K for additional discussion of the Einstein License.

Collaboration Agreement with Merck

On November 14, 2017, we entered into an Exclusive Patent License and Research Collaboration Agreement, or the Merck Collaboration Agreement, with Merck Sharp & Dohme Corp., or Merck, for a partnership to research and develop certain of our proprietary biologics that target certain autoimmune disease indications, or the Initial Indications. We viewed the Merck Collaboration Agreement as a strategic component of our development strategy since it has subsidized the research for and advanced our early autoimmune programs through partnership with a world class pharmaceutical company, while allowing us to continue focusing on our more advanced cancer programs. The research program outlined in the Merck Collaboration

Agreement entailed (1) our research, discovery and development of certain Immuno-STAT drug product candidates up to the point of demonstration of certain biologically relevant effects, or Proof of Mechanism, and (2) the further development by Merck of the Immuno-STAT drug product candidates that have demonstrated Proof of Mechanism, or the Proposed Product Candidates, up to the point of demonstration of all or substantially all of the properties outlined in such Proposed Product Candidates' profiles as described in the Merck Collaboration Agreement. The research collaboration term under the Merck Collaboration Agreement expired on December 31, 2021 and, as of December 20, 2022, the Merck Collaboration Agreement terminated.

For the purposes of this collaboration, we granted to Merck under the Merck Collaboration Agreement an exclusive license under certain of our patent rights, including a sublicense of patent rights licensed from Einstein, to the extent applicable to the specific Immuno-STAT that were elected to be developed by Merck. So long as Merck continued product development on a Proposed Product Candidate, we were restricted from conducting any development activities within the Initial Indication covered by such Proposed Product Candidate other than pursuant to the Merck Collaboration Agreement.

In exchange for the licenses and other rights granted to Merck under the Merck Collaboration Agreement, Merck paid to us a $2.5 million nonrefundable up-front payment. The Merck Collaboration Agreement required us to deploy the first $2.5 million of milestone payments received under the agreement to fund and support contract research. For the years ended December 31, 2022 and 2021, we recorded approximately $0 and $2,155,000, respectively, in collaboration revenue related to the Merck Collaboration Agreement. We did not record short or long-term research and development liabilities on our balance sheet dated December 31, 2022 and December 31, 2021, as the performance obligation was completed on December 31, 2021. The research term and financial support of research conducted under the Merck Collaboration Agreement expired on December 31, 2021, and as of December 20, 2022, all rights granted to Merck under the Merck Collaboration Agreement were returned to us with no further obligations to Merck.

See “Our Collaboration Agreement with Merck” under Part I, Item 1 of the Annual Report on Form 10-K for additional discussion of the Merck Collaboration Agreement.

Collaboration Agreement with LG Chem

Effective November 6, 2018, we entered into a collaboration agreement with LG Chem, Ltd., or LG Chem, which we refer to as the LG Chem Collaboration Agreement, related to the development of Immuno-STATs focused in the field of oncology.

Pursuant to the LG Chem Collaboration Agreement, we granted LG Chem an exclusive license to develop, manufacture and commercialize our lead product, CUE-101, as well as Immuno-STATs that target T cells against two additional cancer antigens, or Product Candidates (to be elected within a defined timeframe), in Australia, Japan, Republic of Korea, Singapore, Malaysia, Vietnam, Thailand, Philippines, Indonesia, China (including Macau and Hong Kong) and Taiwan, which we refer to collectively as the LG Chem Territory. On December 20, 2018, we reported the selection of WT1, as the first target antigen for a Product Candidate under the LG Chem Collaboration Agreement. In June 2021, after ongoing negotiations regarding the selection of the second of the two additional cancer antigens, we decided, along with LG Chem, to allow the defined selection period to expire without a second antigen being selected. We retain rights to develop and commercialize all assets included in the LG Chem Collaboration Agreement in the United States and in global markets outside of the LG Chem Territory. Under the LG Chem Collaboration Agreement, we will engineer the selected Immuno-STATs for up to three alleles, which are expected to include the predominant alleles in the LG Chem Territory, thereby enhancing our market reach by providing for greater patient coverage of populations in global markets, while LG Chem will establish a chemistry, manufacturing and controls, or CMC, process for the development and commercialization of selected Product Candidates. The LG Chem Collaboration Agreement provided LG Chem with the option to select one additional Immuno-STAT for an oncology target, or an Additional Immuno-STAT, for an exclusive worldwide development and commercialization license. On December 18, 2019, we and LG Chem entered into a global license and collaboration agreement, which was amended on November 5, 2020. We refer to such agreement, as amended, as the Global License and Collaboration Agreement. The Global License and Collaboration Agreement supersedes the provisions of the LG Chem Collaboration Agreement related to LG Chem’s option for an Additional Immuno-STAT but generally does not become effective unless and until LG Chem exercises its option, other than certain select provisions including the length of the option period and representations, warranties and covenants of the parties. On April 30, 2021, LG Chem’s option pursuant to the Global License and Collaboration Agreement expired, and accordingly the Global License and Collaboration Agreement no longer contains any material obligations of ours including the option to co-develop and co-commercialize the additional program worldwide.

Under the terms of the LG Chem Collaboration Agreement, LG Chem paid us a $5.8 million non-refundable, non-creditable up-front payment and purchased approximately $5.0 million of shares of our common stock at a price per share

equal to a 20% premium to the volume weighted-average closing price per share over the thirty (30) trading day period immediately prior to the effective date of the LG Chem Collaboration Agreement. We are also eligible to receive additional aggregate payments of up to approximately $400.0 million if certain research, development, regulatory and commercial milestones are successfully achieved. On May 16, 2019, we earned a $2.5 million milestone payment for the FDA's acceptance of the IND for our lead drug product candidate, CUE-101, pursuant to the LG Chem Collaboration Agreement. On December 7, 2020, we earned a $1.25 million milestone payment on the selection of a preclinical candidate pursuant to the LG Chem Collaboration Agreement. On November 23, 2021, we earned a $3.0 million milestone on the confirmation of Collaboration Product Candidate. In addition, the LG Chem Collaboration Agreement also provides that LG Chem will pay us tiered single-digit royalties on net sales of commercialized Product Candidates, or Collaboration Products, in the LG Chem Territory on a product-by-product and country-by-country basis, until the later of expiration of patent rights in a country, the expiration of regulatory exclusivity in such country, or ten years after the first commercial sale of a Collaboration Product in such country, subject to certain royalty step-down provisions set forth in the LG Chem Collaboration Agreement.

Pursuant to the LG Chem Collaboration Agreement, the parties will share research costs related to Collaboration Products, and LG Chem will provide CMC process development for selected Drug Product Candidates and potentially additional downstream manufacturing capabilities, including clinical and commercial supply for Collaboration Products. In return for performing CMC process development, LG Chem is eligible to receive low-single digit royalty payments on the sales of Collaboration Products sold in all countries outside the LG Chem Territory. For the years ended December 31, 2022 and 2021, we recognized revenue of approximately $1,245,000 and approximately $12,786,000, respectively, related to the LG Chem Collaboration Agreement. As of December 31, 2022, we recorded short-term research and development liabilities on our balance sheet of $0. As of December 31, 2021, we recorded short- and long-term research and development liabilities on our balance sheet of approximately $645,000. The majority of the research phase of the LG Chem Collaboration Agreement was substantially complete on March 31, 2022.

The LG Chem Collaboration Agreement includes various representations, warranties, covenants, indemnities and other customary provisions. LG Chem may terminate the LG Chem Collaboration Agreement for convenience or in the event we undergo a change of control on a program-by-program, product-by-product or country-by-country basis, or in its entirety, at any time following the notice period set forth in the LG Chem Collaboration Agreement. Either party may terminate the LG Chem Collaboration Agreement, in its entirety or on a program-by-program, product-by-product or country-by-country basis, in the event of an uncured material breach. The LG Chem Collaboration Agreement is also terminable by either party (i) upon the bankruptcy, insolvency or liquidation of the other party or (ii) for certain activities involving the challenge of certain patents controlled by the other party. Unless earlier terminated, the LG Chem Collaboration Agreement will expire on a product-by-product and country-by-country basis upon the expiration of the applicable royalty term.

See "Our Collaboration Agreement with LG Chem" under Part I, Item 1 of the Annual Report on Form 10-K for additional discussion of the LG Chem Agreement.

Results of Operations

Collaboration Revenue

We have not generated commercial revenue from product sales. To date, we have generated collaboration revenue from the Merck Collaboration Agreement and the LG Chem Collaboration Agreement. Collaboration revenue may vary from period to period depending on the progress of our work in connection with either or both of our collaboration agreements.

Operating Expenses

We generally recognize operating expenses as they are incurred in two general categories, general and administrative expenses and research and development expenses. Our operating expenses also include non-cash components related to depreciation and amortization of property and equipment and stock-based compensation, which are allocated, as appropriate, to general and administrative expenses and research and development expenses.

General and administrative expenses consist of salaries and related expenses for executive, legal, finance, human resources, information technology and administrative personnel, as well as professional fees, insurance costs, and other general corporate expenses. We expect general and administrative expenses to increase in future periods as we incur additional expenses related to our operation as a public company which requires our compliance with certain regulatory and legal procedures. We expect activities supporting our operations including legal, accounting, insurance, employee compensation and other expenses to increase.

Research and development expenses consist primarily of compensation expenses, fees paid to consultants, outside service providers and organizations (including research institutes at universities), facility expenses, and development and

clinical trial expenses with respect to our drug product candidates. We charge research and development expenses to operations as they are incurred. We expect research and development expenses to increase in the future as we continue to advance the clinical development of CUE-101 and CUE-102, including our ongoing and planned clinical trials, and develop potential future drug product candidates based on our technology and research. We also believe that rising inflation, supply chain disruptions and labor shortages may also contribute to increased research and development costs.

Years Ended December 31, 2022 and 2021

Our consolidated statements of operations and comprehensive loss for the years ended December 31, 2022 and 2021, as discussed herein are presented below.

	Years Ended December 31,	
	2022	**2021**
Collaboration revenue	$ 1,245,227	$ 14,941,370
Operating expenses (income):		
General and administrative	16,168,586	17,306,678
Research and development	38,578,083	41,346,765
Gain on right-of-use asset termination	(276,633)	—
Total operating expenses	54,470,036	58,653,443
Loss from operations	(53,224,809)	(43,712,073)
Other income (expense):		
Interest income	928,242	45,898
Interest expense	(713,815)	—
Total other income	214,427	45,898
Loss before provision for income taxes	(53,010,382)	(43,666,175)
Provision for income taxes	—	(495,000)
Net loss	$ (53,010,382)	$ (44,161,175)
Unrealized loss from available-for-sale securities	(95,873)	(7,131)
Comprehensive loss	$ (53,106,255)	$ (44,168,306)
Net loss per common share – basic and diluted	$ (1.49)	$ (1.41)
Weighted average common shares outstanding – basic and diluted	35,649,134	31,285,418

Collaboration Revenue

Collaboration revenue totaled approximately $1,245,000 and $14,941,000 for the years ended December 31, 2022 and 2021, respectively. This decrease of approximately $13,696,000 was due to the expiration of the research collaboration term under the Merck Collaboration Agreement on December 31, 2021 and the completion of the research phase under the LG Chem Collaboration Agreement at March 31, 2022. All collaboration revenue recognized was related to the performance of services under our collaboration agreements with Merck and LG Chem.

General and Administrative

General and administrative expenses totaled approximately $16,169,000 and $17,307,000 for the years ended December 31, 2022 and 2021, respectively. This decrease of approximately $1,138,000 was due primarily to lower professional and consulting fees, rent, stock-based compensation, offset by employee and board compensation and other business expenses related to the ongoing management of the company.

General and administrative expenses for the year ended December 31, 2022 included expenses related to employee and board compensation of $4,766,000 professional and consulting fees of approximately $4,676,000, stock-based compensation of $4,615,000, rent of $899,000, and other general and administrative expenses totaling $1,213,000.

General and administrative expenses for the year ended December 31, 2021 included expenses related to professional and consulting fees of approximately $5,564,000, stock-based compensation of $5,308,000, employee and board compensation of $4,182,000, rent of $1,082,000, and other general and administrative expenses totaling $1,171,000.

Research and Development

Research and development expenses totaled approximately $38,578,000 and $41,347,000 for the years ended December 31, 2022 and 2021, respectively. This decrease of approximately $2,769,000 was due primarily to lower laboratory and drug substance manufacturing costs, other professional fees, licensing fees and rent, offset by employee and Scientific and Clinical Advisory Board compensation.

Research and development expenses for the year ended December 31, 2022 included expenses related to employee and Scientific and Clinical Advisory Board compensation of approximately $10,087,000, research and laboratory expenses of $9,966,000, clinical expenses of $6,690,000, stock-based compensation of $4,881,000, rent of $3,283,000, and other research and development related expenses totaling $3,671,000.

Research and development expenses for the year ended December 31, 2021 included expenses related to research and laboratory expenses of approximately $12,321,000, employee and Scientific and Clinical Advisory Board compensation of $9,634,000, stock-based compensation of $6,208,000, clinical expenses of $4,301,000, rent of $3,881,000, and other research and development related expenses of $5,002,000.

Gain on Right-of-use Asset Termination

Gain on right-of-use asset termination was approximately $277,000 and $0 for the years ended December 31, 2022 and 2021, respectively. This increase of $277,000 for the year ended December 31, 2022, as compared to the year ended December 31, 2021, was due to the gain on right-of-use asset related to the termination of our operating lease agreement for our laboratory and office space in Cambridge, Massachusetts at 21 Erie Street, effective on April 30, 2022, and the termination of our lease agreement for additional procedure and holding rooms in Cambridge, Massachusetts effective December 6, 2022.

Interest Income

Interest income was approximately $928,000 for the year ended December 31, 2022, as compared to approximately $46,000 for the year ended December 31, 2021. Interest income for the year ended December 31, 2022 included approximately $437,000 in income resulting from amortization of discounts received on certain of our marketable securities, approximately $170,000 of interest income from our operating sweep account, and approximately $321,000 from amortization/accretion on investments, compared to approximately $46,000 of other income for the year ended December 31, 2021.

Foreign Withholding Taxes

Provision for income tax for the years ended December 31, 2022 and 2021 was comprised of $0 and approximately $495,000, respectively, in foreign income tax expense on LG Chem milestone payments in each year.

Interest Expense

Interest expense was approximately $714,000 and $0 for the years ended December 31, 2022 and 2021, respectively. This increase of $714,000 was primarily due to cash paid for interest expense related to the proceeds from borrowings under our Loan and Security Agreement, or the Loan Agreement, with Silicon Valley Bank, or SVB, of $679,000, and amortization of deferred issuance costs of $31,000.

Net Loss

As a result of the foregoing, our net loss was approximately $53,010,000 for the year ended December 31, 2022, as compared to approximately $44,161,000 for the year ended December 31, 2021.

Liquidity and Capital Resources

We have financed our working capital requirements primarily through private and public offerings of equity securities, cash received from Merck and LG Chem under the respective collaboration agreements and borrowings under the Loan Agreement. At December 31, 2022 and December 31, 2021, we had cash, cash equivalents and marketable securities totaling approximately $76,289,000 and approximately $64,400,000, respectively, available to fund our ongoing business activities. Additional information concerning our financial condition and results of operations is provided in the financial statements included in this Annual Report on Form 10-K.

The amounts that we actually spend for any specific purpose may vary significantly and will depend on a number of factors, including, but not limited to, our research and development activities and programs, clinical testing, regulatory approval, market conditions, and changes in or revisions to our business strategy and technology development plans.

On June 22, 2020, we filed a registration statement on Form S-3ASR, which became automatically effective upon filing with the SEC (File No. 333-239357), or the 2020 Shelf, to register for sale from time to time up to $300.0 million of our common stock, preferred stock, debt securities, warrants, rights and/or units in one or more offerings.

In June 2020, we entered into an ATM equity offering sales agreement, or the June 2020 ATM Agreement, with Stifel Nicolaus & Company, Inc., or Stifel, to sell shares of our common stock for aggregate gross proceeds of up to $40.0 million, from time to time, through an "at-the-market" equity offering program under which Stifel acted as sales agent. As of December 31, 2022, we had sold 907,700 shares of common stock under the June 2020 ATM Agreement for proceeds of $10.4 million, net of commissions paid, but excluding transaction expenses. The June 2020 ATM Agreement was terminated prior to entering into the October 2021 ATM Agreement (as defined below).

In October 2021, we entered into an open market sale agreement, or the October 2021 ATM Agreement, with Jefferies LLC, or Jefferies, to sell shares of our common stock for aggregate gross proceeds of up to $80.0 million, from time to time, through an ATM equity offering program under which Jefferies acts as sales agent. The October 2021 ATM Agreement will terminate upon the earliest of (a) the sale of $80.0 million of shares of our common stock pursuant to the October 2021 ATM Agreement or (b) the termination of the October 2021 ATM Agreement by us or Jefferies. As of December 31, 2022, we had sold an aggregate of 3,593,407 shares of common stock under the October 2021 ATM Agreement for proceeds of $23.6 million, net of commissions paid, but excluding transaction expenses.

On February 15, 2022, we entered into the Loan Agreement, pursuant to which we have borrowed $10.0 million. The term loans under the Loan Agreement, or the Term Loans, bear interest at a floating rate per annum equal to the greater of (A) the prime rate (as published in the money rates section of The Wall Street Journal) plus 2.25% and (B) 5.50%. On the first calendar day of each month, we will be required to make monthly interest payments and commencing on June 30, 2023 (extended to December 31, 2023 if the additional term loans are advanced), we will be required to repay the Term Loans in (i) 30 consecutive installments of principal plus monthly payments of accrued interest if the additional term loans are not advanced and (ii) 24 months if the additional term loans are advanced. All outstanding principal and accrued and unpaid interest under the Term Loans and all other outstanding obligations with respect to the Term Loans are due and payable in full on December 1, 2025.

The Loan Agreement permits voluntary prepayment of all, but not less than all, of the Term Loans, subject to a prepayment premium except if the facility is refinanced with another SVB facility. Such prepayment premium would be 3.00% of the principal amount of the Term Loans if prepaid prior to the first anniversary of the date on which we entered the Loan Agreement, 2.00% of the principal amount of the Term Loan if prepaid on or after the first anniversary of the date on which we entered the Loan Agreement but prior to the second anniversary of the date on which we entered the Loan Agreement, and 1.00% of the principal amount of the Term Loan if prepaid on or after the second anniversary of the date on which we entered the Loan Agreement. Upon prepayment or repayment in full of the Term Loans, we will be required to pay a one-time final payment fee equal to 5.00% of the original principal amount of any funded Term Loans being repaid. The Loan Agreement also requires us to maintain in accounts at the Lender unrestricted and unencumbered cash equal to the lesser of all of our cash and 110% of the obligations to the Lender.

On March 10, 2023, SVB was closed and the FDIC was appointed receiver for the bank. The FDIC created a successor bridge bank, Silicon Valley Bridge Bank, N.A., or SVBB, and all deposits of SVB were transferred to SVBB under a systemic risk exception approved by the United States Department of the Treasury, the Federal Reserve and the FDIC. SVBB continues to hold our Term Loans under the same existing terms and covenants which were in place with SVB. The vast majority of the Company's cash, cash equivalents and marketable securities reside in custodial accounts at US Bank for which SVB Asset Management is the advisor.

On November 14, 2022, we entered into securities purchase agreements with accredited investors pursuant to which on November 16, 2022, we issued and sold to such investors in a private placement an aggregate of 7,656,966 shares of common stock and, in lieu of shares of common stock to certain investors, pre-funded warrants, or Pre-Funded Warrants, to purchase an aggregate of 1,531,440 shares of common stock, and, in each case, accompanying warrants, or Warrants, to purchase an aggregate of up to 9,188,406 additional shares of common stock (or Pre-Funded Warrants in lieu thereof) at a price of $3.265 per share and accompanying Warrant (or $3.2649 per Pre-Funded Warrant and accompanying Warrant), or the PIPE Financing. The exercise price of the Warrants is $3.93 per share, or if exercised for a Pre-Funded Warrant in lieu thereof, $3.9299 per Pre-Funded Warrant. The Warrants are exercisable at any time after they are issued and ending on the fifth

anniversary of the closing. The Pre-Funded Warrants are exercisable at any time after they are issued and will not expire. We received aggregate gross proceeds from the PIPE Financing of approximately $30 million, before deducting placement agent fees and offering expenses of $2.6 million. Piper Sandler & Co. acted as lead placement agent and Public Ventures LLC acted as co-placement agent for the PIPE Financing.

If we issue additional equity securities to raise funds, the ownership percentage of our existing stockholders would be reduced. New investors may demand rights, preferences or privileges senior to those of existing holders of our common stock. If we issue debt securities, we may be required to grant security interests in our assets, could have substantial debt service obligations, and lenders may have a senior position (compared to stockholders) in any potential future bankruptcy or liquidation. Additionally, corporate collaboration and licensing arrangements may require us to incur non-recurring and other charges, give up certain rights relating to our intellectual property and research and development activities, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, issue debt which may require liens on our assets and which will increase our monthly expense obligations, or disrupt our management and business.

Cash Flows

The following table summarizes our changes in cash, cash equivalents, and restricted cash for the year ended December 31, 2022 and 2021:

	December 31,	
	2022	2021
Net cash provided by (used in):		
Operating activities	$ (41,805,954)	$ (38,837,166)
Investing activities	(24,609,877)	9,108,511
Financing activities	53,659,133	19,233,322
Net decrease in cash, cash equivalents, and restricted cash	$ (12,756,698)	$ (10,495,333)

Operating Activities

During the year ended December 31, 2022, we used cash of approximately $41,806,000 in operating activities, as compared to approximately $38,837,000 of cash used in operating activities during the year ended December 31, 2021. Cash used during the year ended December 31, 2022 consisted primarily of our net loss of approximately $53,010,000, and decreases of approximately $1,071,000 in accrued expenses, $735,000 in operating lease liability, $645,000 in research and development contract liabilities, $395,000 in deposits, $321,000 in amortization of premium/discount on purchased securities, and $277,000 on gain on right-of-use asset modification. Cash used was partially offset by increases of approximately $9,496,000 in stock-based compensation expense, $3,085,000 in accounts receivable, $922,000 in depreciation and amortization, $884,000 operating lease right-of-use asset, $109,000 in accretion of final payment of term loan, $83,000 in accounts payable, $34,000 in prepaids and other assets, $31,000 in amortization of debt issuance costs, and $4,000 on loss on disposal of fixed asset.

Cash used during the year ended December 31, 2021 consisted primarily of our net loss of approximately $44,161,000, and decreases of approximately $7,973,000 in research and development contract liabilities, $3,036,000 in operating lease right-of-use asset, $1,725,000 in accounts receivable, $200,000 in prepaid expense and deposits, $22,000 on gain on disposal of fixed asset, and $5,000 in amortization of premium/discount on purchased securities. Cash used was partially offset by increases of approximately $11,516,000 in stock-based compensation expense, $2,907,000 in operating lease liability, $1,833,000 in accrued expenses, approximately $1,258,000 in depreciation and amortization, $250,000 in other assets as well as $520,000 in accounts payable.

Investing Activities

During the year ended December 31, 2022, our investing activities used approximately $24,610,000 in cash, compared to cash generated by investing activities of approximately $9,109,000 during the year ended December 31, 2021. Cash used during the year ended December 31, 2022 consisted primarily of approximately $29,445,000 for the purchase of marketable securities, and purchases of property and equipment of $171,000, offset by $5,000,000 for the redemption of marketable securities, and the cash received for sale of fixed assets of approximately $6,000. Cash generated during the year ended December 31, 2021, consisted primarily of approximately $10,000,000 for the redemption of marketable securities, cash received for sale of fixed assets of approximately $22,000, offset by the purchase of property and equipment of approximately $913,000.

Financing Activities

During the year ended December 31, 2022, we generated cash from financing activities of approximately $53,659,000, compared to approximately $19,233,000 during the year ended December 31, 2021. Cash generated during the year ended December 31, 2022 consisted primarily of cash proceeds from the common stock sold through the October 2021 ATM Agreement of approximately $16,599,000, net of underwriting commissions and fees, cash proceeds from the sale of common stock in the PIPE Financing, net of fees of $22,702,000, cash proceeds from the sale of pre-funded warrants in the PIPE Financing of $4,700,000, net of fees, and $10,000,000 of proceeds from borrowing under the term loan, offset by restricted stock awards net of taxes withheld of $200,000 and $142,000 for the payment of debt issuance costs. Cash generated during the year ended December 31, 2021 consisted primarily of cash proceeds from the common stock sold through our ATM sales agreements with Stifel and Jefferies of approximately $17,385,000, net of underwriting commissions and fees, and the exercise of common stock options of approximately $2,599,000, offset by restricted stock awards net of taxes withheld of $750,000.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of our Immuno-STAT platform, continue ongoing and initiate new clinical trials of and seek marketing approval for our drug product candidates. In addition, we expect to incur additional costs associated with operating as a public company. Our expenses will also increase if, and as, we:

- continue the clinical development of our CUE-100 series, including CUE-101 and CUE-102;
- leverage our programs to advance our other drug product candidates into preclinical and clinical development;
- seek regulatory approvals for any drug product candidates for which we successfully complete clinical trials;
- seek to discover and develop additional drug product candidates in the CUE-100 series, including Neo-STATs;
- establish a sales, marketing, medical affairs and distribution infrastructure to commercialize any drug product candidates for which we may obtain marketing approval and intend to commercialize on our own or jointly;
- hire additional clinical, quality control and scientific personnel;
- expand our manufacturing, quality, operational, financial and management systems;
- increase personnel, including personnel to support our clinical development, manufacturing and commercialization efforts and our operations as a public company;
- maintain, expand and protect our intellectual property portfolio;
- acquire or in-license other drug product candidates and technologies; and
- incur additional legal, accounting and other expenses in operating as a public company.

In the first quarter of 2022, we determined to prioritize and strategically focus on our CUE-101 and CUE-102 oncology programs in our CUE-100 series. We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop CUE-103 and our Neo-STAT and RDI-STAT programs, as well as our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series. In 2022, we also determined to take proactive steps to decrease our office and lab footprint and to restructure our research and development functions in support of prioritized corporate objectives and strategies. These steps have realized cost savings to date that have been allocated to our key programs.

We believe that our existing cash, cash equivalents and marketable securities as of December 31, 2022 will enable us to fund our operating requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

We will need to raise additional capital or incur indebtedness to continue to fund our operations in the future. Our ability to raise additional funds will depend on financial, economic and market conditions, many of which are outside of our control, and we may be unable to raise financing when needed, or on terms favorable to us. If we are unable to raise additional

funds when needed, we may be required to delay, reduce or eliminate our product development or future commercialization efforts, or grant rights to develop and market drug product candidates that we would otherwise prefer to develop and market ourselves, which could adversely affect our business prospects, and we may be unable to continue our operations. Because of numerous risks and uncertainties associated with the research, development and commercialization of our drug product candidates, we are unable to estimate the exact amount of our working capital requirements. Factors that may affect our planned future capital requirements and accelerate our need for additional working capital include the following:

- the progress, timing, scope and costs of our clinical trials, including the ability to timely enroll patients in our planned and potential future clinical trials;
- the outcome, timing and cost of regulatory approvals by the FDA and other comparable regulatory authorities, including the potential that the FDA or other comparable regulatory authorities may require that we perform more studies than those that we currently expect;
- the number and characteristics of drug product candidates that we may in-license and develop;
- our ability to successfully commercialize our drug product candidates, if approved;
- the amount of sales and other revenues from drug product candidates that we may commercialize, if any, including the selling prices for such potential products and the availability of adequate third-party reimbursement;
- selling and marketing costs associated with our potential products, including the cost and timing of expanding our marketing and sales capabilities;
- the terms and timing of any potential future collaborations, licensing or other arrangements that we may establish;
- cash requirements of any future acquisitions and/or the development of other drug product candidates;
- the costs of operating as a public company;
- the cost and timing of completion of commercial-scale, outsourced manufacturing activities;
- the time and cost necessary to respond to technological and market developments;
- any disputes which may occur between us and Einstein, employees, collaborators or other prospective business partners; and
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

A change in the outcome of any of these or other variables with respect to the development of any of our drug product candidates could significantly change the costs and timing associated with the development of that drug product candidate. Further, our operating plans may change in the future, and we may need additional funds to meet operational needs and capital requirements associated with such operating plans.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings, collaborations, strategic partnerships or marketing, distribution or licensing arrangements with third parties and grants from organizations and foundations. If we raise additional funds by selling shares of our common stock or other equity-linked securities, the ownership interest of our current stockholders will be diluted. We may seek to access the public or private capital markets whenever conditions are favorable, even if we do not have an immediate need for additional capital at that time. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or drug product candidates or to grant licenses on terms that may not be acceptable to us. If we raise additional funds through debt financing, we may have to grant a security interest on our assets to the future lenders, our debt service costs may be substantial, and the lenders may have a preferential position in connection with any future bankruptcy or liquidation.

If we are unable to raise additional capital when needed, we may be required to curtail the development of our technology or materially curtail or reduce our operations. We could be forced to sell or dispose of our rights or assets. Any inability to raise adequate funds on commercially reasonable terms could have a material adverse effect on our business, results

of operation and financial condition, including the possibility that a lack of funds could cause our business to fail, dissolve and liquidate with little or no return to investors.

Principal Commitments

Leased Facilities

On March 28, 2022, we entered into a License Agreement, or the License, with MIL 40G, LLC, or the Licensor, pursuant to which we lease approximately 13,000 square feet of office, research and development and laboratory space located at 40 Guest Street, Boston, Massachusetts 02135, or the Premises. We relocated our corporate headquarters to the Premises in April 2022. On March 28, 2022, we terminated our operating lease agreement for laboratory and office space in Cambridge, Massachusetts at 21 Erie Street, or the Laboratory and Office Lease, with an effective termination date of April 30, 2022. We performed an analysis of the accounting implications of this termination based on ASC 360 Impairments and Abandonments guidance. For the year ended December 31, 2022, we recorded an adjustment to decrease the right-of-use asset and lease liability of approximately $8,124,000 and $8,382,000, respectively, and recorded a gain on right-of-use asset included in the consolidated statement of operations and other comprehensive loss of approximately $258,000.

We recognized a right of use asset of approximately $9,056,000 and an operating lease liability of approximately $9,056,000 which were recorded as of the Term Commencement Date (as defined below) related to the License.

The term of the License commenced on April 15, 2022, or the Term Commencement Date, and expires on April 14, 2026, or the Term. The License has a monthly rental rate of $200,700 for the first year of the Term, $208,728 for the second year of the Term, $217,077 for the third year of the Term and $225,760 for the remainder of the Term. Pursuant to the License, we prepaid two months of rent and a security deposit. The Licensor is obligated under the License to provide certain services to us, including providing certain gases, chemicals and equipment to the Premises' laboratory space, IT support, security, office support and health and safety training. The Licensor has the right to terminate the License for Cause (as defined in the License).

On May 3, 2022, we entered into the First Amendment to the License, or the First Amendment, with the Licensor, pursuant to which the License was expanded to include an additional room effective July 15, 2022. In consideration of the First Amendment, the security deposit was increased from $225,760 to $235,884 effective July 15, 2022. Upon execution of the First Amendment, we prepaid three months of rent, two of which will be held in escrow and credited against future rent payments and the other of which was applied to the first month's rent. Effective July 15, 2022, the monthly rental rate under the First Amendment increased to $209,700 from $200,700. During the year ended December 31, 2022, we recognized a right of use asset of approximately $369,000 and a short and long term operating lease liability of approximately $100,300 and $260,600, respectively, using the weighted average discount rate of 8%, which were recorded as of the Term Commencement Date related to the License.

On May 31, 2022, we entered into an operating lease for additional laboratory space at 40 Guest Street, Boston, Massachusetts for the period from December 1, 2022, through December 1, 2024, or the 40G Additional Laboratory Lease. The 40G Additional Laboratory Lease contains escalating payments during the lease period. The monthly rental rate under the 40G Additional Laboratory Lease is $59,152 for the first 12 months and $61,519 for the remainder of the term. Under the terms of this lease agreement, we prepaid three months of rent, two of which will be held in escrow and credited against future rent payments and the other of which was applied to the first month's rent. During the year ended December 31, 2022, we recognized a right of use asset of approximately $1,307,000 and a short and long term operating lease liability of approximately $712,000, and $535,000, respectively, using the weighted average discount rate of 10%, which were recorded as of the Term Commencement Date related to the License.

On September 9, 2022, we terminated our lab space lease in Cambridge, Massachusetts with MIL 21E, LLC with an effective termination date of December 6, 2022. We performed an analysis of the accounting implications of this termination based on ASC 360 Impairments and Abandonments guidance. During the year ended December 31, 2022, we recorded an entry to remove the remaining lease liability and right of use asset of $963,000 and $945,000, respectively. The difference between the carrying amounts of the right of use asset and lease liability of $19,000 was recorded to gain on right of use asset termination and included in the consolidated statement of operations.

For the year ended December 31, 2022, we recorded approximately $626,000 in interest expense to the lease liability.

At December 31, 2022, we recorded approximately $9,203,000 to operating lease right-of-use asset, and approximately $3,300,000 and $6,018,000 to the short-term and long-term operating lease liability, respectively. At December 31, 2021, we recorded approximately $9,809,876 to operating lease right-of-use asset, and approximately $4,931,675 and

$5,121,179 to short- and long-term operating lease liability, respectively. As of December 31, 2022 and 2021, a security deposit of approximately $794,000 was included in deposits on the consolidated balance sheet related to the 40G Additional Laboratory Lease. Cash was collected in the amount of approximately $803,000 for the 21 Erie Laboratory and Office Lease during the year ended December 31, 2022.

Manufacturing Agreement with Catalent

We entered into an agreement with Catalent Pharma Solutions, LLC or Catalent, for Catalent to provide us with contracted manufacturing services related to the manufacture of CUE-102 materials. At December 31, 2022, we have committed to contract manufacturing services totaling approximately $2,423,000 in which work will begin in January 2023.

Einstein License Agreement

Our commitments with respect to the Einstein License are summarized above at "Significant Contracts and Agreements Related to Research and Development Activities".

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

As a smaller reporting company, as defined by Rule 12b-2 of the Exchange Act, we are not required to provide the information under this item.

Item 8. Financial Statements and Supplementary Data.

Our financial statements and the related notes, together with the Report of Independent Registered Public Accounting Firm thereon, are set forth beginning on page F-1 of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

As of the end of the period covered by this report, management performed, with the participation of our principal executive and principal financial officers, an evaluation of the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, to allow timely decisions regarding required disclosures. Based on the evaluation, our principal executive and principal financial officers concluded that, as of December 31, 2022, our disclosure controls and procedures were effective.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Rule 13a-15(f) of the Exchange Act. Management evaluated the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control Integrated Framework (the 2013 Framework). Based on this assessment, our management concluded that, as of December 31, 2022, our internal control over financial reporting was effective based on those criteria. All internal control systems, no matter how well designed, have inherent limitations. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. There were no changes in our internal control over financial reporting during the fiscal quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

As a non-accelerated filer and a "smaller reporting company", as defined in Rule 12b-2 under the Exchange Act, our independent registered public accounting firm is not required to issue an attestation report on the internal control over financial reporting.

Item 9B. Other Information.

Not applicable.

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

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item is incorporated by reference to our Definitive Proxy Statement on Schedule 14A relating to our 2023 annual meeting of stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 11. Executive Compensation

The information required by this Item (other than the information required by Item 402(v) of Regulation S-K) is incorporated by reference to our Proxy Statement on Schedule 14A relating to our 2023 annual meeting of stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholders Matters.

The information required by this Item is incorporated by reference to our Proxy Statement on Schedule 14A relating to our 2023 annual meeting of stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated by reference to our Proxy Statement on Schedule 14A relating to our 2023 annual meeting of stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 14. Principal Accountant Fees and Services

The information required by this Item is incorporated by reference to our Proxy Statement on Schedule 14A relating to our 2023 annual meeting of stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Cue Biopharma, Inc.

Opinion on the Financial Statements
We have audited the accompanying consolidated balance sheets of Cue Biopharma, Inc. and its subsidiary (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for the years then ended, and the related notes to the consolidated financial statements (collectively, the financial statements). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for the years then ended, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion
These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

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

Evaluation of the Company's Ability to Continue as a Going Concern
As discussed in Note 1 of the consolidated financial statements, the Company is in the development stage and has incurred recurring losses and negative cash flows from operations since inception and expects to incur additional loses in the future. Additionally, the Company's Term Loan Agreement contains customary representations, warranties, events of default and covenants, including a requirement that the Company maintain in accounts at the Lender unrestricted and unencumbered cash equal to the lesser of all the Company's cash and 110% of the obligations to the Lender. As of December 31, 2022, the Company had cash, cash equivalents and marketable securities of approximately $76.3 million. Management believes that current cash, cash equivalents and marketable securities on hand at December 31, 2022 are sufficient to fund operations for at least the next twelve months from the date of issuance of these financial statements; however, the future viability of the Company is dependent on its ability to raise additional capital to finance its operations and to fund research and development costs in order to seek approval for commercialization of its drug product candidates.

We identified the evaluation of the Company's ability to continue as a going concern as a critical audit matter due to the high degree of auditor judgment in evaluating the uncertainty regarding the Company's future cash flows and the risk of bias in management's judgements and assumptions in estimating these cash flows.

Our audit procedures related to the Company's assertion of its ability to continue as a going concern included the following, among others:

- Evaluated the Company's forecasted working capital, operating expenses, and uses and sources of cash within management's assessment of whether the Company has sufficient liquidity to fund operations for at least one year from the financial statement issuance date. This testing included:
  - Comparing prior period forecasts to actual results.
  - Developing an understanding of management's expectations for future changes through inquiry and review of budgets.
  - Evaluating the positive and negative evidence impacting management's forecasts, the Company's financing arrangements in place as of the report date, market and industry factors and the Company's relationship with its financing partner.
- Evaluated subsequent event activity related to additional cash available or needed to fund working capital requirements.
- Evaluated the completeness and accuracy of the Company's disclosures.

/s/ RSM US LLP

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

Boston, Massachusetts
March 21, 2023

CUE BIOPHARMA, INC.

CONSOLIDATED BALANCE SHEETS

	December 31,	
	2022	2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 51,614,102	$ 64,370,800
Marketable securities	24,674,903	—
Accounts receivable	57,252	3,142,527
Prepaid expenses and other current assets	841,217	954,792
Total current assets	77,187,474	68,468,119
Property and equipment, net	1,499,263	2,111,949
Operating lease right-of-use asset	9,202,670	9,809,876
Deposits	3,115,712	2,720,991
Restricted cash	150,000	150,000
Other long term assets	128,333	140,000
Total assets	$ 91,283,452	$ 83,400,935
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,731,123	$ 2,590,701
Accrued expenses	3,554,211	4,619,963
Research and development contract liability, current portion	—	645,344
Operating lease liabilities, current portion	3,300,173	4,931,675
Current portion of long-term debt, net	1,963,028	—
Total current liabilities	11,548,535	12,787,684
Operating lease liabilities, net of current portion	6,017,613	5,121,179
Long-term debt, net	8,034,729	—
Total liabilities	25,600,877	17,908,863
Commitments and contingencies (Note 15)		
Stockholders' equity:		
Preferred stock, $0.001 par value, authorized – 10,000,000 shares; issued and outstanding – none	—	—
Common stock, $0.001 par value; authorized – 100,000,000 shares; issued and outstanding – 43,042,548 shares and 32,202,496 shares at December 31, 2022 and 2021, respectively	43,042	32,202
Additional paid-in capital	316,192,002	262,906,084
Accumulated other comprehensive income	(95,873)	—
Accumulated deficit	(250,456,596)	(197,446,214)
Total stockholders' equity	65,682,575	65,492,072
Total liabilities and stockholders' equity	$ 91,283,452	$ 83,400,935

See accompanying notes to consolidated financial statements.

CUE BIOPHARMA, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

	Years Ended December 31,	
	2022	**2021**
Collaboration revenue	$ 1,245,227	$ 14,941,370
Operating expenses (income):		
General and administrative	16,168,586	17,306,678
Research and development	38,578,083	41,346,765
Gain on right-of-use asset termination	(276,633)	—
Total operating expenses	54,470,036	58,653,443
Loss from operations	(53,224,809)	(43,712,073)
Other income (expense):		
Interest income	928,242	45,898
Interest expense	(713,815)	—
Total other income	214,427	45,898
Loss before provision for income taxes	$ (53,010,382)	$ (43,666,175)
Provision for income taxes	—	(495,000)
Net loss	$ (53,010,382)	$ (44,161,175)
Unrealized loss from available-for-sale securities	(95,873)	(7,131)
Comprehensive loss	$ (53,106,255)	$ (44,168,306)
Net loss per common share – basic and diluted	$ (1.49)	$ (1.41)
Weighted average common shares outstanding – basic and diluted	35,649,134	31,285,418

See accompanying notes to consolidated financial statements.

CUE BIOPHARMA, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Par Value				
Balance, December 31, 2020	30,351,366	$ 30,351	$ 232,159,029	$ 7,131	$ (153,285,039)	$ 78,911,472
Issuance of common stock from ATM offering, net of sales agent commission and fees	1,383,887	1,384	17,383,284	—	—	17,384,668
Stock-based compensation	—	—	11,515,584	—	—	11,515,584
Exercise of stock options	382,219	382	2,598,400	—	—	2,598,782
Issuance of common stock upon exercise of warrants, net	8,048	8	(8)	—	—	—
Restricted stock awards released	131,667	132	(77)	—	—	55
Restricted stock awards withheld at vesting to cover taxes	(54,691)	(55)	(750,128)	—	—	(750,183)
Unrealized losses from available-for-sale securities	—	—	—	(7,131)	—	(7,131)
Net loss	—	—	—	—	(44,161,175)	(44,161,175)
Balance, December 31, 2021	32,202,496	$ 32,202	$ 262,906,084	$ —	$ (197,446,214)	$ 65,492,072
Issuance of common stock from ATM offering, net of sales agent commission and fees	3,117,220	3,117	16,595,294	—	—	16,598,411
Issuance of common stock and pre-funded warrants, net of issuance costs	7,656,966	7,657	27,394,687	—	—	27,402,344
Stock-based compensation	—		9,495,876	—	—	9,495,876
Issuance of common stock upon exercise of warrants, net	9,549	10	(10)	—	—	—
Restricted stock awards released	98,335	98	(56)	—	—	42
Restricted stock awards withheld at vesting to cover taxes	(42,018)	(42)	(199,873)	—	—	(199,915)
Unrealized losses from available-for-sale securities	—	—	—	(95,873)	—	(95,873)
Net loss	—	—	—	—	(53,010,382)	(53,010,382)
Balance, December 31, 2022	43,042,548	$ 43,042	$ 316,192,002	$ (95,873)	$ (250,456,596)	$ 65,682,575

See accompanying notes to consolidated financial statements.

CUE BIOPHARMA, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Years Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (53,010,382)	$ (44,161,175)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	922,216	1,257,662
Stock-based compensation	9,495,876	11,515,584
Amortization of operating lease right-of-use asset	883,839	(3,035,647)
Amortization of premium/discount on purchased securities	(320,612)	(4,581)
Gain on right-of-use asset modification	(276,633)	—
Loss on disposal of fixed asset	3,962	(21,550)
Amortization of debt issuance costs	30,810	—
Accretion of final payment of term loan	108,696	—
Changes in operating assets and liabilities:		
Account receivable	3,085,275	(1,725,045)
Prepaid expenses and other current assets	33,602	(50,434)
Other assets	—	250,000
Deposits	(394,721)	(148,515)
Accounts payable	83,110	520,398
Accrued expenses	(1,070,580)	1,832,752
Research and development contract liability, current portion	(645,344)	(7,973,255)
Operating lease liability	(735,068)	2,906,640
Net cash used in operating activities	(41,805,954)	(38,837,166)
Cash flows from investing activities:		
Purchases of property and equipment	(170,746)	(913,039)
Cash received from sale of fixed asset	6,205	21,550
Redemption of marketable securities	5,000,000	10,000,000
Purchases of marketable securities	(29,445,336)	—
Net cash (used in) provided by investing activities	(24,609,877)	9,108,511
Cash flows from financing activities:		
Proceeds from ATM offering, net of sales agent commission and fees	16,598,411	17,384,668
Proceeds from common stock issuance, net of transaction costs	22,702,345	—
Proceeds from pre-funded warrant issuance, net of transaction costs	4,699,999	—
Proceeds from borrowing under term loan	10,000,000	—
Proceeds from the exercise of stock options	—	2,598,782
Payment of debt issuance costs	(141,749)	—
Restricted stock awards withheld at vesting to cover taxes	(199,873)	(750,128)
Net cash provided by financing activities	53,659,133	19,233,322
Net decrease in cash, cash equivalents, and restricted cash	(12,756,698)	(10,495,333)
Cash, cash equivalents, and restricted cash at beginning of year	64,520,800	75,016,133
Cash, cash equivalents, and restricted cash at end of year	$ 51,764,102	$ 64,520,800
Supplemental disclosures of cash flow information:		
Purchases of property and equipment in accounts payable or accrued expenses	$ 57,312	$ —
Cash paid for interest	$ 570,347	$ —
Right-of-use asset and lease liability (new lease)	$ 10,732,858	$ —
Operating lease modification	$ 8,082,551	$ 7,616,000

See accompanying notes to consolidated financial statements.

1. Organization and Basis of Presentation

Cue Biopharma, Inc. (the "Company") was incorporated in the State of Delaware on December 31, 2014 under the name Imagen Biopharma, Inc., and completed its organization, formation and initial capitalization activities effective as of January 1, 2015. In October 2016, the Company changed its name to Cue Biopharma, Inc. The Company's corporate office and research facilities are located in Boston, Massachusetts.

The Company is a clinical-stage biopharmaceutical company developing a novel class of injectable biologics designed to selectively engage and modulate tumor-specific T cells within the body to treat a broad range of cancers, chronic infectious diseases, and autoimmune diseases.

The Company is in the development stage and has incurred recurring losses and negative cash flows from operations since inception. As of December 31, 2022, the Company had cash, cash equivalents and marketable securities of approximately $76.3 million. Management believes that current cash, cash equivalents and marketable securities on hand at December 31, 2022 are sufficient to fund operations for at least the next twelve months from the date of issuance of these financial statements; however, the future viability of the Company is dependent on its ability to raise additional capital to finance its operations and to fund research and development costs in order to seek approval for commercialization of its drug product candidates. The Company's failure to raise capital as and when needed would have a negative impact on its financial condition and its ability to pursue its business strategies as this capital is necessary for the Company to perform the research and development activities required to develop the Company's drug product candidates in order to generate future revenue streams.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements for the years ended December 31, 2022 and 2021, have been prepared in accordance with the rules and regulations of the Securities and Exchange Commission (the "SEC") and Generally Accepted Accounting Principles in the United States ("U.S. GAAP") for financial information, which prescribes elimination of all significant intercompany accounts and transactions in the accounts of the Company and its wholly owned subsidiary, Cue Biopharma Securities Corp., which was incorporated in the Commonwealth of Massachusetts in December 2018. In the opinion of management, these financial statements reflect all adjustments which are necessary for a fair statement of the Company's financial position and results of its operations, as of and for the periods presented.

Public Offerings

In June 2020, the Company entered into an at-the-market ("ATM") equity offering sales agreement (the "June 2020 ATM Agreement") with Stifel Nicolaus & Company, Inc. ("Stifel") to sell shares of the Company's common stock for aggregate gross proceeds of up to $40 million, from time to time, through an ATM equity offering program under which Stifel would act as sales agent. As of December 31, 2022, the Company sold an aggregate 2,099,700 shares of common stock under the June 2020 ATM Agreement for proceeds of approximately $32.7 million, net of commissions paid, but excluding transaction expense. The June 2020 ATM Agreement terminated in October 2021 prior to entering into the October 2021 ATM Agreement (as defined below).

In October 2021, the Company entered into an open market sale agreement (the "October 2021 ATM Agreement") with Jefferies LLC ("Jefferies"), as agent, to sell shares of the Company's common stock for aggregate gross proceeds of up to $80 million, from time to time, through an ATM equity offering program. The October 2021 ATM Agreement will terminate upon the earliest of (a) the sale of $80 million of shares of the Company's common stock pursuant to the October 2021 ATM Agreement or (b) the termination of the October 2021 ATM Agreement by the Company or Jefferies. During the year ended December 31, 2022, the Company sold 3,117,220 shares of common stock under the October 2021 ATM Agreement for proceeds of approximately $16.6 million, net of commissions paid, but excluding transaction expense. As of December 31, 2022, the Company sold an aggregate 3,593,407 shares of common stock under the October 2021 ATM Agreement for proceeds of approximately $23.6 million, net of commissions paid, but excluding transaction expenses, since its inception.

Issuance of Securities through a Private Placement

On November 14, 2022, the Company entered into securities purchase agreements with accredited investors pursuant to which, on November 16, 2022, the Company issued and sold to such investors in a private placement an aggregate of 7,656,966 shares of common stock and, in lieu of shares of common stock to certain investors, pre-funded warrants (or "Pre-Funded Warrants") to purchase an aggregate of 1,531,440 shares of common stock, and, in each case, accompanying warrants, or Warrants, to purchase an aggregate of up to 9,188,406 additional shares of common stock (or Pre-Funded Warrants in lieu thereof) at a price of $3.265 per share and accompanying Warrant (or $3.2649 per Pre-Funded Warrant and accompanying Warrant), (such financing, the "PIPE Financing"). The exercise price of the Warrants is $3.93 per share, or if exercised for a Pre-Funded Warrant in lieu thereof, $3.9299 per Pre-Funded Warrant. The Warrants are exercisable at any time after they are issued and ending on the fifth anniversary of the closing. The Pre-Funded Warrants are exercisable at any time after they are issued and will not expire. The Company received aggregate gross proceeds from the PIPE Financing of approximately $30 million, before deducting placement agent fees and offering expenses of approximately $2.6 million. Piper Sandler & Co. acted as lead placement agent and Public Ventures LLC acted as co-placement agent for the PIPE Financing.

The Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the Warrants do not provide any guarantee of value or return at December 31, 2022, the weighted average exercise price is $3.93 and the weighted average contractual life is five years. The Pre-Funded Warrants do not have an expiration date.

The Pre-Funded Warrants met the permanent equity criteria classification. The Pre-Funded Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the Pre-Funded Warrants do not provide any guarantee of value or return.

Consolidation

The accompanying consolidated financial statements include the Company and its wholly owned subsidiary, Cue Biopharma Securities Corp. The Company has eliminated all intercompany transactions.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Significant estimates include estimates related to collaboration revenue, the accounting for potential liabilities and accrued expenses, the assumptions utilized in valuing stock-based compensation issued for services, the realization of deferred tax assets, and the useful life with respect to long-lived assets and intangibles. Actual results could differ from those estimates.

COVID-19 Pandemic

The extent to which the COVID-19 pandemic may continue to impact the Company’s business and financial results will depend on numerous evolving factors including, but not limited to: the extent of its impact on worldwide macroeconomic conditions, the speed of the anticipated recovery, access to capital markets, and governmental and business policies regarding the pandemic. The Company assessed certain accounting matters that generally require consideration of forecasted financial information in context with the information reasonably available to the Company and the unknown future impacts of the COVID-19 pandemic as of December 31, 2022 and through the date of the filing of this Annual Report on Form 10-K. The accounting matters assessed included, but were not limited to, estimates related to collaboration revenue, the accounting for potential liabilities and accrued expenses, the assumptions utilized in valuing stock-based compensation issued for services, the realization of deferred tax assets, and assessments of impairment related to long-lived assets and intangibles. The Company’s future assessment of the potential effects of the COVID-19 pandemic, as well as other factors, could result in material impacts to the Company’s consolidated financial statements in future reporting periods.

Despite the Company’s efforts, the impact of the COVID-19 pandemic on its business depends on factors beyond the Company’s knowledge or control, including the supply-chain disruptions, as well as third-party actions taken to contain its spread and mitigate its public health effects. As a result, the Company is unable to estimate the extent to which the COVID-19 pandemic may negatively impact its financial results or liquidity in the future.

Cash Concentrations

The Company maintains its cash balances with a financial institution in federally insured accounts and may periodically have cash balances in excess of insurance limits. The Company maintains its accounts with a financial institution with a high credit rating. The Company has not experienced any losses to date and believes that it is not exposed to any significant credit risk on cash. On March 10, 2023, one of the financial institutions the Company has accounts with, Silicon Valley Bank ("SVB"), was closed and the FDIC was appointed receiver for the bank. The FDIC created a successor bridge bank, Silicon Valley Bridge Bank, N.A. (“SVBB”), and all deposits of SVB were transferred to SVBB under a systemic risk exception approved by the United States Department of the Treasury, the Federal Reserve and the FDIC. See further discussion in Note 18.

Cash and Cash Equivalents

The Company considers all highly liquid investments with a maturity of three months or less at the date of purchase to be cash equivalents. The Company currently invests available cash in money market funds.

Marketable Securities

Marketable securities consist of investments with original maturities greater than ninety days and less than one year from the balance sheet date. The Company classifies all of its investments as available-for-sale securities. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are recognized and determined on a specific identification basis and are included in other comprehensive loss. Realized gains and losses are determined on a specific identification basis and are included in other income on the consolidated statement of operations and comprehensive loss. Amortization and accretion of discounts and premiums is recorded in interest income. The Company has invested available cash in U.S. Treasury obligations.

Restricted Cash

The Company had $150,000 in restricted cash deposited with a commercial bank to collateralize a credit card as of December 31, 2022 and 2021.

Property and Equipment

Property and equipment is recorded at cost. Major improvements are capitalized, while maintenance and repairs are charged to expense as incurred. Gains and losses from dispositions of property and equipment are included in income and expense when realized. Amortization of leasehold improvements is provided using the straight-line method over the shorter of the lease term or the useful life of the underlying assets. Depreciation of property and equipment is provided using the straight-line method over the following estimated useful lives:

Laboratory equipment	5 years
Computer equipment	3 years
Furniture and fixtures	3-8 years

The Company recognizes depreciation and amortization expense in general and administrative expenses and in research and development expenses in the Company’s consolidated statements of operations and comprehensive loss, depending on how each category of property and equipment is utilized in the Company’s business activities.

Trademark

Trademark consists of the Company’s right, title and interest to the CUE BIOLOGICS Mark, and any derivative mark incorporating CUE, throughout the world, together with all associated goodwill and common law rights appurtenant thereto, including, but not limited to, any right, title and interest in any corporate name, company name, business name, trade name, dba, domain name, or other source identifier incorporating CUE.

The Company has classified the trademark as a component of other long-term assets, having a useful life of 15 years. The Company evaluates the status of this intangible asset for amortization and impairment at each year end reporting date. The Company recorded $11,666 in amortization related to the trademark at December 31, 2022 and 2021.

Debt Issuance Costs

Debt issuance costs are deferred and presented as a reduction to long-term debt. Debt issuance costs are amortized using the effective interest rate method over the term of the loan. Amortization of deferred debt issuance costs are included in interest expense in the consolidated statements of operations and other comprehensive loss.

Revenue Recognition

The Company recognizes collaboration revenue under certain of the Company's license and collaboration agreements that are within the scope of Accounting Standards Codification ("ASC"), Topic 606, *Revenue from Contracts with Customers* ("ASC 606"). The Company's contracts with customers typically include promises related to licenses to intellectual property and research and development services. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenue from non-refundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. Accordingly, the transaction price is generally comprised of a fixed fee due at contract inception and variable consideration in the form of milestone payments due upon the achievement of specified events and tiered royalties earned when customers recognize net sales of licensed products. The Company measures the transaction price based on the amount of consideration to which it expects to be entitled in exchange for transferring the promised goods and/or services to the customer. The Company utilizes the "most likely amount" method to estimate the amount of variable consideration, to predict the amount of consideration to which it will be entitled for its one open contract. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved. At the inception of each arrangement that includes development and regulatory milestone payments, the Company evaluates whether the associated event is considered probable of achievement and estimates the amount to be included in the transaction price using the most likely amount method.

Research and Development Expenses

Research and development expenses consist primarily of compensation costs, fees paid to consultants, outside service providers and organizations (including research institutes at universities), facility costs, and development and clinical trial costs with respect to the Company's drug product candidates.

Research and development expenses incurred under contracts are expensed ratably over the life of the underlying contracts, unless the achievement of milestones, the completion of contracted work, or other information indicates that a different pattern of performance is more appropriate. Other research and development expenses are charged to operations as incurred.

Nonrefundable advance payments are recognized as an expense as the related services are performed. The Company evaluates whether it expects the services to be rendered at each quarter end and year end reporting date. If the Company does not expect the services to be rendered, the advance payment is charged to expense. Nonrefundable advance payments for research and development services are included in prepaid and other current assets on the balance sheet. To the extent that a nonrefundable advance payment is for contracted services to be performed within 12 months from the reporting date, such advance is included in current assets; otherwise, such advance is included in non-current assets.

The Company evaluates the status of its research and development agreements and contracts, and the carrying amount of the related assets and liabilities, at each quarter end and year end reporting date, and adjusts the carrying amounts and their classification on the balance sheet as appropriate.

Patent Expenses

The Company is the exclusive worldwide licensee of, and has patent applications pending for, numerous domestic and foreign patents. Due to the significant uncertainty associated with the successful development of one or more commercially viable drug product candidates based on the Company's research efforts and any related patent applications, all patent costs, including patent-related legal fees, filing fees and other costs are charged to general and administrative expense as incurred. For the years ended December 31, 2022 and 2021, patent expenses were approximately $2,142,000 and $2,259,000, respectively.

Licensing Fees and Costs

Licensing fees and costs consist primarily of costs relating to the acquisition of the Company's license agreement (the "Einstein License Agreement") with the Albert Einstein College of Medicine ("Einstein"), including related royalties, maintenance fees, milestone payments and product development costs. Licensing fees and costs are charged to research and development expense as incurred.

Long-Lived Assets

The Company reviews long-lived assets, consisting of property and equipment, for impairment at each fiscal year end or when events or changes in circumstances indicate the carrying value of these assets may exceed their current fair values. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, an impairment charge is recognized for the amount by which the carrying amount of the asset exceeds the fair value of the assets. Assets to be disposed of are separately presented in the balance sheet and reported at the lower of the carrying amount or fair value less costs to sell and are no longer depreciated. The Company has not historically recorded any impairment to its long-lived assets. In the future, if events or market conditions affect the estimated fair value to the extent that a long-lived asset is impaired, the Company will adjust the carrying value of these long-lived assets in the period in which the impairment occurs. During the year ended December 31, 2022, the Company sold furniture and fixtures and lab equipment with an acquisition cost of $43,000 and collected cash of $6,200. The Company recorded a loss on the sale of fixed assets of $4,000, which is presented in other income on the consolidated statement of operations and other comprehensive loss. During the year ended December 31, 2021, the Company sold fully depreciated lab equipment with an acquisition cost of $271,820, and the Company recorded a gain on the sale of fixed assets of $21,550, which is presented in other income on the consolidated statements of operations and other comprehensive loss.

Leases

The Company accounts for leases under ASC 842 Leases, which requires a lessee to record a right-of-use asset and a corresponding lease liability for most lease arrangements on the balance sheet. Under the standard, disclosure of key information about leasing arrangements to assist users of the financial statements with assessing the amount, timing and uncertainty of cash flows arising from leases are required.

Stock-Based Compensation

The Company periodically issues stock-based awards to officers, directors, employees, Scientific and Clinical Advisory Board members and consultants for services rendered. Such issuances vest and expire according to terms established at the issuance date.

Stock-based payments to officers, directors, employees, Scientific and Clinical Advisory Board members and consultants, including grants of employee stock options, are recognized in the financial statements based on their grant date fair values. Stock option grants, which are generally time-vested, are measured at the grant date fair value and charged to operations on a straight-line basis over the service period, which generally approximates the vesting term. The Company also grants performance-based awards periodically to officers of the Company. The Company recognizes compensation costs related to performance awards over the requisite service period if and when the Company concludes that it is probable that the performance condition will be achieved.

The fair value of stock options and restricted stock units is determined utilizing the Black-Scholes option-pricing model, which is affected by several variables, including the risk-free interest rate, the expected dividend yield, the life of the equity award, the exercise price of the stock option as compared to the fair value of the common stock on the grant date, and the estimated volatility of the common stock over the term of the equity award.

The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant. Until the Company has established a trading history for its common stock that approximates the expected term of the options, estimated volatility is based on the average historical volatilities of comparable public companies in a similar industry. The expected dividend yield is based on the current yield at the grant date; the Company has never declared or paid dividends and has no plans to do so for the foreseeable future. As permitted by Staff Accounting Bulletin No. 107, due to the Company's limited trading history and option activity, management utilizes the simplified method to estimate the expected term of options at the date of grant.

The Company recognizes the fair value of stock-based compensation in general and administrative expenses and in research and development expenses in the Company's consolidated statements of operations and comprehensive loss, depending on the type of services provided by the recipient of the equity award.

Income Taxes

The Company accounts for income taxes under an asset and liability approach for financial accounting and reporting for income taxes. Accordingly, the Company recognizes deferred tax assets and liabilities for the expected impact of differences between the financial statements and the tax basis of assets and liabilities.

The Company accounts for uncertainties in income tax law under a comprehensive model for the financial statement recognition, measurement, presentation and disclosure of uncertain tax positions taken or expected to be taken in income tax returns as prescribed by U.S. GAAP. The tax effects of a position are recognized only if it is "more-likely-than-not" to be sustained by the taxing authority as of the reporting date. If the tax position is not considered "more-likely-than-not" to be sustained, then no benefits of the position are recognized.

The Company records a valuation allowance to reduce its deferred tax assets to the amount that is more likely than not to be realized. In the event the Company was to determine that it would be able to realize its deferred tax assets in the future in excess of its recorded amount, an adjustment to the deferred tax assets would be credited to operations in the period such determination was made. Likewise, should the Company determine that it would not be able to realize all or part of its deferred tax assets in the future, an adjustment to the deferred tax assets would be charged to operations in the period such determination was made.

The Company is subject to U.S. federal and Massachusetts state income taxes. As the Company's net operating losses have yet to be utilized, all previous tax years remain open to examination by federal and state taxing authorities in which the Company currently operates.

For the year ended December 31, 2022, there is no provision for income taxes in the U.S. because the Company has historically incurred net operating losses and maintains a full valuation allowance against its net deferred assets. The reported amount of income tax expense for the years differs from the amount that would result from applying domestic federal statutory tax rates to pretax losses primarily because of changes in valuation allowance. The Company recognized approximately $495,000 of income tax expense related to the foreign taxes withheld from an upfront payment received from LG Chem, Ltd. ("LG Chem") pursuant to a collaboration agreement with LG Chem (the "LG Chem Collaboration Agreement") during the year ended December 31, 2021.

The Company recognizes interest accrued relative to unrecognized tax benefits in interest expense and penalties in operating expense. During the years ended December 31, 2022 and 2021, the Company did not recognize any income tax related interest and penalties. The Company did not have any accruals for income tax related interest and penalties at December 31, 2022 and 2021.

Comprehensive Income (Loss)

Components of comprehensive income or loss, including net income or loss, are reported in the financial statements in the period in which they are recognized. Other comprehensive income or loss is defined as the change in equity during a period from transactions and other events and circumstances from non-owner sources. Net income (loss) and other comprehensive income (loss) are reported net of any related tax effect to arrive at comprehensive income (loss). Comprehensive income (loss) includes net income (loss) as well as changes in stockholders' equity that result from transactions and economic events other than those with stockholders. The Company's only element of other comprehensive income (loss) in periods presented was unrealized gain or loss on available-for-sale securities.

Earnings (Loss) Per Share

The Company's computation of earnings (loss) per share ("EPS") for the respective periods includes basic and diluted EPS. Basic EPS is measured as the income (loss) attributable to common stockholders divided by the weighted average number of common shares outstanding for the period. Diluted EPS is similar to basic EPS but presents the dilutive effect on a per share basis of potential common shares that would result from the exercise of outstanding stock options and warrants as if they had been exercised at the beginning of the periods presented, or issuance date, if later. Potential common shares that have an anti-dilutive effect (i.e., those that increase income per share or decrease loss per share) are excluded from the calculation of diluted EPS. Basic and diluted loss per common share is the same for all periods presented because all outstanding stock options and warrants are anti-dilutive.

At December 31, 2022 and 2021, the Company excluded the outstanding securities summarized below, which entitled the holders thereof to acquire shares of common stock, from its calculation of earnings per share, as their effect would have been anti-dilutive.

	December 31,	
	2022	2021
Common stock warrants	10,719,846	851,969
Common stock options	6,740,122	5,654,168
Nonvested restricted stock units	—	98,335
Total	17,459,968	6,604,472

Fair Value of Financial Instruments

The authoritative guidance with respect to fair value established a fair value hierarchy that prioritizes the inputs to valuation techniques used to measure fair value into three levels and requires that assets and liabilities carried at fair value be classified and disclosed in one of three categories, as presented below.

Level 1. Observable inputs such as quoted prices in active markets for an identical asset or liability that the Company has the ability to access as of the measurement date. Financial assets and liabilities utilizing Level 1 inputs include active-exchange traded securities and exchange-based derivatives.

Level 2. Inputs, other than quoted prices included within Level 1, which are directly observable for the asset or liability or indirectly observable through corroboration with observable market data. Financial assets and liabilities utilizing Level 2 inputs include fixed income securities, non-exchange based derivatives, mutual funds, and fair-value hedges.

Level 3. Unobservable inputs in which there is little or no market data for the asset or liability which requires the reporting entity to develop its own assumptions. Financial assets and liabilities utilizing Level 3 inputs include infrequently-traded non-exchange-based derivatives and commingled investment funds and are measured using present value pricing models.

The Company determines the level in the fair value hierarchy within which each fair value measurement falls in its entirety, based on the lowest level input that is significant to the fair value measurement in its entirety. In determining the appropriate levels, the Company performs an analysis of the assets and liabilities at each reporting period end.

The Company had approximately $45,423,000 in cash equivalents and approximately $24,675,000 in short-term marketable securities that were measured and recorded at fair value on the Company’s balance sheet at December 31, 2022. The Company had approximately $52,509,000 in cash equivalents and $0 in short-term marketable securities that were measured and recorded at fair value on the Company’s balance sheet at December 31, 2021.

The carrying value of financial instruments (consisting of cash, a certificate of deposit, debt, accounts payable, accrued compensation and accrued expenses) is considered to be representative of their respective fair values due to the short-term nature of those instruments.

Recent Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board (the "FASB") issued Accounting Standards Update ("ASU") No. 2016-13, *Financial Instruments- Credit Losses: Measurement of Credit Losses on Financial Instruments* (Topic 326) (CECL). The new standard requires entities to measure all expected credit losses for financial assets held at the reporting date based on historical experience, current conditions and reasonable and supportable forecasts. The new standard is effective for annual reporting periods beginning after December 15, 2022, including interim reporting periods within each annual reporting period for smaller reporting companies. The Company adopted ASU 2016-13 but there was no financial impact to the Company's consolidated financial statements for the year ended December 31, 2022.

Management does not believe that any other recently issued, but not yet effective, authoritative guidance, if currently adopted, would have a material impact on the Company’s financial statement presentation or disclosures.

3. Fair Value

The Company accounts for its financial assets and liabilities using fair value measurements. The authoritative accounting guidance defines fair value, establishes a framework for measuring fair value under U.S. GAAP and enhances disclosures about fair value measurements. Fair value is defined as the exchange price that would be received for an asset or

paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date.

The following table presents information about the Company's assets that are measured at fair value on a recurring basis as of December 31, 2022 and 2021 and indicate the level of the fair value hierarchy utilized to determine such fair value:

	Fair Value Measurements as of December 31, 2022			
	Level 1	Level 2	Level 3	Fair Value
Cash equivalents	$ 45,423,219	$ —	$ —	$ 45,423,219
Marketable securities	24,674,903	—	—	24,674,903
Total	$ 70,098,122	$ —	$ —	$ 70,098,122

	Fair Value Measurements as of December 31, 2021			
	Level 1	Level 2	Level 3	Fair Value
Cash equivalents	$ 52,509,287	$ —	$ —	$ 52,209,287
Marketable securities	—	—	—	—
Total	$ 52,509,287	$ —	$ —	$ 52,209,287

As of December 31, 2022 , the Company reported approximately $45,423,000 and $24,675,000 in cash equivalents and marketable securities, respectively. The Company measures the cash equivalents that are invested in money market funds using Level 1 inputs for identical securities. The Company measures the fair value of marketable securities that are invested in U.S. Treasury securities using Level 2 inputs and primarily relies on quoted prices in active markets for similar marketable securities. As of December 31, 2021, the Company reported approximately $52,209,000 of cash equivalents. During the years ended December 31, 2022 and 2021, there were no transfers between Level 2 and Level 3.

The carrying values of accounts receivable, prepaid expenses, other current assets, debt, accounts payable and accrued expenses approximate their fair value due to the short-term nature of these balances.

4. Marketable Securities

As of December 31, 2022, the Company had marketable securities in the amount of $24,674,903. The Company did not have marketable securities at December 31, 2021. The following table presents the Company's marketable securities at December 31, 2022:

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. Treasury Securities	$ 24,770,776	$ —	$ (95,873)	$ 24,674,903
	$ 24,770,776	$ —	$ (95,873)	$ 24,674,903

At December 31, 2022, the Company's marketable securities consisted of $24,770,776 of investments that mature within 12 months and the Company recorded an unrealized loss on investments of $95,873 for the year ended December 31, 2022. At December 31, 2021, the Company had no marketable securities and recorded an unrealized loss on investments of $7,131 for the year ended December 31, 2021.

5. Property and Equipment

Property and equipment as of December 31, 2022 and 2021 consisted of the following:

	December 31,	
	2022	2021
Laboratory equipment	$ 5,246,029	$ 5,203,166
Furniture and fixtures	80,568	93,322
Computer equipment	296,342	252,804
Leasehold-Improvements	117,821	6,530
	5,740,760	5,555,822
Less accumulated depreciation	(4,241,497)	(3,443,873)
Net property and equipment	$ 1,499,263	$ 2,111,949

Depreciation expense for the year ended December 31, 2022 was included in the consolidated statements of operations and comprehensive loss as follows, excluding trademark amortization of $11,666 and amortization of capitalized license expenses of $79,973. Depreciation expense for the year ended December 31, 2021 was included in the consolidated statements of operations and comprehensive loss as follows, excluding trademark amortization of $11,666 and amortization of capitalized license expenses of $336,882.

	Years Ended December 31,	
	2022	2021
General and administrative	$ 14,704	$ 14,401
Research and development	815,873	894,713
Total	$ 830,577	$ 909,114

During the year ended December 31, 2022, the Company sold furniture and fixtures and lab equipment with an acquisition cost of $43,119 and collected cash of $6,205, and recorded a loss on the sale of fixed assets of $3,962. During the year ended December 31, 2021, the Company sold fully depreciated lab equipment with an acquisition cost of $271,820, and the Company recorded a gain on the sale of fixed assets of $21,500, which is presented in other income on the consolidated statements of operations and other comprehensive loss.

6. Loan with Silicon Valley Bank

On February 15, 2022 (the “Closing Date”), the Company entered into a Loan and Security Agreement (the “Term Loan Agreement”), with Silicon Valley Bank, as lender (“Lender”). The Company drew $10,000,000 in term loans under the Term Loan Agreement (the "Term Loans") on the Closing Date.

The Term Loans bear interest at a floating rate per annum equal to the greater of (A) the prime rate (as published in the money rates section of The Wall Street Journal) plus 2.25% and (B) 5.50%. The Term Loans are interest only from the Closing Date through June 30, 2023, after which the Company is required to pay 30 equal monthly installments of principal. At December 31, 2022, the interest rate was 9.75% based on the prime rate plus 2.25%.

The Term Loans may be prepaid in full prior to February 15, 2024 with payment of a 2.00% prepayment premium, on or after which they may be prepaid in full with payment of a 1.00% prepayment premium. Upon prepayment or repayment in full of the Term Loans, the Company will be required to pay a one-time final payment fee equal to 5.00% of the original principal amount of any funded Term Loans being repaid. This one-time final payment fee is recorded to interest expense using the effective interest method over the period of the Term Loans in the consolidated statements of operation and other comprehensive loss.

The Term Loans and related obligations under the Term Loan Agreement are secured by substantially all of the Company's properties, rights and assets, except for its intellectual property which is subject to a negative pledge under the Term Loan Agreement.

The Term Loan Agreement contains customary representations, warranties, events of default and covenants, including a requirement that the Company maintain in accounts of the Company at the Lender unrestricted and unencumbered cash equal to the lesser of all of the Company's cash and 110% of the obligations to the Lender. On March 10, 2023, SVB was closed by state regulators and the FDIC was appointed receiver for the bank. The FDIC created a successor bridge bank, Silicon Valley Bridge Bank, N.A. ("SVBB") and all deposits of SVB were transferred to SVBB under a systemic risk exception approved by the United States Department of the Treasury, the Federal Reserve and the FDIC. SVBB continues to hold the Company's Term Loans under the same existing terms and covenants which were in place with SVB.

During the years ended December 31, 2022 and 2021, the Company recognized interest expense related to the Term Loans of $570,347 and $0, respectively, and $108,695 and $0, respectively, in interest expense related to accretion of the final payment.

The following table presents the aggregate maturities of Long-term debt as of December 31, 2022 (in thousands):

Year	Aggregate Minimum Payments
2023	$ 2,000
2024	4,000
2025	4,000
Total maturities	$ 10,000

Total long-term debt	$ 8,000
Accretion of final payment	109
Less: unamortized debt issuance costs	(74)
Long-term debt, net	$ 8,035
Total current portion of long-term debt	$ 2,000
Less: unamortized debt issuance costs	(37)
Current portion of long-term debt, net	$ 1,963

Debt Issuance Costs

Debt issuance costs are deferred and presented as a reduction to long-term debt. Debt issuance costs are amortized using the effective interest rate method over the term of the loan. Amortization of deferred debt issuance costs are included in interest expense in the consolidated statements of operations and comprehensive loss. The Company incurred approximately $141,748 in debt issuance costs related to the Term Loan Agreement. For the year ended December 31, 2022, the Company recorded $30,810 in amortization of debt issuance costs to interest expense in the consolidated statements of operations and comprehensive loss. The Company recorded $73,967 and $36,972 to short- and long-term debt issuance costs contra-liability, respectively, as of December 31, 2022.

7. Accrued Expenses

Accrued expenses as of December 31, 2022 and 2021 is summarized as follows:

	December 31,	
	2022	2021
Employee and board compensation	$ 2,273,250	$ 2,006,465
Contract manufacturing services	—	1,273,978
Professional services	242,617	352,114
Contract research services	1,038,344	987,406
	$ 3,554,211	$ 4,619,963

8. Einstein License and Service Agreement

License Agreement

On January 14, 2015, the Company entered into a license agreement, as amended on June 2, 2015 (the "Einstein License"), with Albert Einstein College of Medicine ("Einstein") for certain patent rights relating to the Company's core technology platform for the engineering of biologics to control T cell activity, precision, immune-modulatory drug product candidates, and two supporting technologies that enable the discovery of costimulatory signaling molecules (ligands) and T-cell targeting peptides. On July 31, 2017, the Company entered into an amended and restated license agreement which modified certain obligations of the parties under the Einstein License.

Under the Einstein License, the Company holds an exclusive worldwide license, with the right to sublicense, import, make, have made, use, provide, offer to sell, and sell all products, processes and services that use the patents covered by the Einstein License, including certain technology received from Einstein relating thereto (the "Licensed Products"). Under the Einstein License, the Company is required to:

- Pay royalties and amounts based on certain percentage of proceeds, as defined in the Einstein License, from sales of Licensed Products and sublicense agreements.
- Pay escalating annual maintenance fees, which are nonrefundable, but are creditable against the amount due to Einstein for royalties.
- Make significant payments based upon the achievement of certain milestones, as defined in the Einstein License. Payments made upon achievement of milestones are nonrefundable and are not creditable against any other payment due to Einstein. At December 31, 2022, $1,233,367 had been incurred by the Company since inception towards achievement of these milestones.
- Incur minimum product development costs until the first commercial sale of the first licensed product.

The Company was in compliance with its obligations under the Einstein License at December 31, 2022 and 2021.

The Einstein License expires upon the expiration of the Company's last obligation to make royalty payments to Einstein which may be due with respect to certain Licensed Products, unless terminated earlier under the provisions thereof. The Einstein License includes certain termination provisions if the Company fails to meet its obligations thereunder.

Pursuant to the Einstein License, the Company issued to Einstein 671,572 shares of the Company's common stock in connection with the consummation of the initial public offering of its common stock on December 27, 2017.

The Company accounts for license fees incurred in connection with the Einstein License in accordance with ASC 730, *Research and Development*. Please refer to Note 11 Collaboration Agreement with LG Chem.

9. Stock-Based Compensation

Effective March 23, 2016, the Company adopted the 2016 Omnibus Incentive Plan (the "Omnibus Plan") and the 2016 Non-Employee Equity Incentive Plan (the "Non-Employee Plan"), which are intended to allow the Company to compensate and retain the services of key employees, non-employees, Scientific and Clinical Advisory Board members, and outside advisors and consultants. The plans are under the administration of the Company's Board of Directors. Under the plans, the Company, at its discretion, may grant stock option awards to certain employees and non-employees through March 23, 2026. The Omnibus Plan and the Non-Employee Plan initially provided for the grant of a total of 2,000,000 shares of common stock and 500,000 shares of common stock, respectively.

On August 13, 2017, the Company's Board of Directors approved an amendment and restatement of the Company's Omnibus Plan to increase the number of shares authorized for issuance under such plan by 800,000 shares, from 2,000,000 shares to 2,800,000 shares, subject to stockholder approval of such amendment within 12 months following board approval thereof. The Company's stockholders approved the plan in December 2017. Additionally, on May 17, 2019, the Company's Board of Directors approved Amendment No. 1 to the Omnibus Plan to increase the number of shares that may be issued as incentive stock options under the plan, which the Company's stockholders approved on August 6, 2019. The Omnibus Plan, as amended and restated, provides that on the first day of each fiscal year of the Company during the period beginning in fiscal year ended December 31, 2018 and ending on the second day of fiscal year ending December 31, 2027, the number of shares of common stock authorized to be issued under such plan shall be increased by an amount equal to the lesser of (i) the number of shares necessary such that the aggregate number of shares available to be issued under the plan equals 20% of the number of fully diluted outstanding shares on such date (assuming the conversion of all outstanding shares of preferred stock and other outstanding convertible securities and exercise of all outstanding options and warrants to purchase shares) and (ii) an amount to be determined by the Company's Board of Directors.

Pursuant to the plans, during the year ended December 31, 2022, the Company granted stock options to purchase 828,500 shares of the Company's common stock and 0 restricted stock units, 0 shares of common stock were exercised, 308,801 shares of common stock were cancelled, and 98,335 restricted stock units were released. At December 31, 2022, stock options for 4,032,146 shares of common stock and 320,000 restricted stock units had been granted and 560,855 shares of common stock were reserved for future grants under the Omnibus Plan, and stock options for 494,600 shares of common stock had been granted and 5,400 shares of common stock were reserved for future grants under the Non-Employee Plan. In the aggregate, at December 31, 2022, stock options for a total of 4,526,746 shares of common stock and 320,000 restricted stock units had been granted and 566,255 shares of common stock were reserved for future grants. Such grants are accounted for as share-based compensation in accordance with ASC 718, *Compensation - Stock Compensation*, and ASC 505-50, *Equity-Based Payments to Non-Employees*.

Stock Option Valuation

For stock options requiring an assessment of value during the years ended December 31, 2022 and 2021, the fair value of each stock option award was estimated using the Black-Scholes option-pricing model utilizing the following assumptions:

	December 31,	
	2022	**2021**
Risk-free interest rate	1.53 to 2.92%	0.61 to 1.43%
Expected dividend yield	0%	0%
Expected volatility	92.1-95.7%	92.8-100.9%
Expected life	5.5 to 6.25 years	5.5 to 6.25 years

The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant for periods corresponding with the expected term of the stock option award; as permitted by Staff Accounting Bulletin 107, due to insufficient history of stock option activity, management has utilized the simplified approach to estimate the expected term of the stock options, which represents the period of time that stock options granted are expected to be outstanding; the expected volatility is based upon historical volatilities of comparable companies in a similar industry; and the expected dividend yield based upon the Company's current dividend rate and future expectations.

A summary of stock option activity for the years ended December 31, 2022 and 2021 is as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in Years)
Stock options outstanding at December 31, 2020	5,030,899	$ 9.10	5.51
Granted	1,251,000	13.88	
Exercised	(382,219)	6.80	
Cancelled	(245,512)	14.42	
Stock options outstanding at December 31, 2021	5,654,168	10.08	5.48
Granted	828,500	6.99	
Exercised	—	—	
Cancelled	(308,801)	11.32	
Stock options outstanding at December 31, 2022	6,173,867	9.60	5.05
Stock options exercisable at December 31, 2022	4,397,991	$ 9.04	3.74

The Company recognized, $8,649,803 and $9,588,811, in stock-based compensation during the years ended December 31, 2022 and 2021, respectively, related to stock option activity. As of December 31, 2022, total unrecognized stock-based compensation was approximately $11,743,927, which is expected to be recognized as an operating expense in the Company's consolidated statements of operations and comprehensive loss through December 2025 or 1.94 years.

The aggregate intrinsic value of exercisable but unexercised in-the-money stock options at December 31, 2022 was approximately $4,397,991 based on a weighted average exercise price of $9.04 per share. The aggregate intrinsic value of options is calculated as the difference of the market close price of $2.85 on December 31, 2022, and the weighted average exercise price of $9.04, with a weighted average remaining contractual term of 3.74 years.

The aggregate intrinsic value of exercisable but unexercised in-the-money stock options at December 31, 2021 was approximately $14,442,527 based on a weighted average exercise price of $8.31 per share at December 31, 2021.

Option Amendments - Modification of Incentive Stock Options

During the year ended December 31, 2022, no option modifications occurred.

During the year ended December 31, 2021, the following event resulted in the amendment to terms of outstanding stock option awards:

On August 20, 2021, an employee who was employed for a particular role pursuant to an employment agreement that prescribed certain separation benefits to the employee was separated from that role. Per the employment agreement, upon termination (i) all unvested stock options would accelerate and become vested as of the termination date, and (ii) the options would remain exercisable, to the extent applicable, following the date of termination for the period prescribed in the equity award plan. As of August 20, 2021, the terminated employee held outstanding options to purchase an aggregate of 117,500 shares of the Company's common stock at a weighted average exercise price of $9.35 per share, including unvested options to purchase 52,500 shares at a weighted average exercise price of $14.98 per share. On August 20, 2021, the unvested portion of the outstanding options vested, and the post-employment option exercise period was extended from 90 days, as prescribed to the equity award plan, to 36 months from the date of the termination.

The Company calculated the change in stock-based compensation cost associated with the previously described stock option modifications pursuant to the applicable guidance in ASC 718. The change in compensation cost was determined by calculating the difference between (a) the estimated fair value of each option award immediately prior to the modifications and (b) the estimated fair value of each option award immediately after the modifications. The fair value of each option award immediately prior to and immediately after modification was estimated using the Black-Scholes option-pricing model to determine an incremental fair value, consistent with and in accordance with the Company's existing accounting policy for stock compensation. The total additional compensation cost associated with the previously described modifications was determined to be approximately $256,074, which was expensed in the year ended December 31, 2021.

Restricted Stock Units

On October 3, 2019, the Company granted 100,000 restricted stock units ("RSUs") with time-based vesting conditions to an executive officer having an average grant date fair value of $7.53 per share. The RSUs vested in three equal installments beginning on the grant date, and annually on each anniversary of the grant date thereafter. Compensation expense is recognized on a straight-line basis.

On February 5, 2020, the Company granted 150,000 RSUs with time-based vesting conditions to an executive officer. One-half of the RSUs vested on September 30, 2021, and the balance vested on March 31, 2022. On March 31, 2020, the Company granted 50,000 RSUs with time-based vesting conditions to an executive officer. The RSUs vested in three equal installments beginning on the grant date, and annually on each anniversary of the grant date thereafter. Compensation expense is recognized on a straight-line basis.

On August 21, 2020, the Company granted 20,000 RSUs with time-based vesting conditions to an executive officer. The RSUs vest in three equal installments beginning on the grant date, and annually on each anniversary of the grant date thereafter, subject to the recipient's continued service on each applicable vesting date. Compensation expense is recognized on a straight-line basis.

The following table summarizes the RSU activity under the Omnibus Plan for the year ending December 31, 2022:

Restricted Securities	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Nonvested balance at December 31, 2021	98,335	$ 18.21
Vested/Released	(98,335)	$ 18.21
Nonvested balance at December 31, 2022	0	$ -

The Company recognized $846,073 and $1,926,773 in stock-based compensation during the years ended December 31, 2022 and 2021, respectively, related to RSU activity. As of December 31, 2022, total unrecognized stock-based compensation was $0.

Stock-based Compensation

Stock-based compensation for the years ended December 31, 2022 and 2021 was included in the consolidated statements of operations and comprehensive loss as follows:

	December 31,	
	2022	2021
General and administrative	$ 4,614,974	$ 5,307,982
Research and development	4,880,902	6,207,602
Total	$ 9,495,876	$ 11,515,584

10. Warrants

The Company has one tranche of common stock warrants outstanding at December 31, 2022. The Company issued warrants exercisable for 1,500 shares of common stock on June 15, 2015 with an exercise price of $2.70 per share, which warrants expired at the end of their 7-year term on June 15, 2022. The Company issued another tranche of warrants exercisable for an aggregate of 882,071 shares of common stock with an exercise price of $9.38 per share when issued on December 27, 2017, which warrants expired at the end of their 5-year term on December 26, 2022. On November 16, 2022 the Company issued 9,188,406 warrants with an exercise price of $3.93 and 1,531,440 Pre-Funded Warrants. The intrinsic value of exercisable but unexercised in-the-money common stock warrants at December 31, 2022 was approximately $0 based on a fair value of $2.85 per share on December 31, 2022.

Each tranche of warrants was evaluated under ASC 480, Distinguishing Liabilities from Equity, and ASC 815, Derivatives and Hedging, and the Company determined that equity classification was appropriate. The Company determined equity classification for both warrants and Pre-Funded Warrants as they do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. Per ASC 815-40-25, the Company will account for the warrants and Pre-Funded Warrants as equity, as the Company does not provide to the holder a fixed or guaranteed return.

The Company recorded cash received from 9,188,406 warrants to purchase shares of common stock and 1,531,440 Pre-Funded Warrants to additional paid in capital in the amount of $27,394,687, net of placement fees of $2,597,649. The Company recorded placements fees and expenses related to the sale of warrants to purchase shares of common stock and Pre-Funded Warrants as a debit to additional paid in capital in the consolidated balance sheet.

The following table summarizes common stock warrant activity for the year ended December 31, 2022:

	Warrant Issued June 15, 2015	Warrant Issued December 27, 2017	Warrant Issued November 16, 2022	Total
Balance at December 31, 2021	62,611	789,358	—	851,969
Issued via cashless exercises	(9,549)	—	—	(9,549)
Withheld as payment to cover issued shares	(51,562)	—	—	(51,562)
Expired	(1,500)	(789,358)	—	(790,858)
Issued	—	—	10,719,846	10,719,846
Balance at December 31, 2022	—	—	10,719,846	10,719,846

11. Collaboration Revenue

The Company recognizes collaboration revenue under certain of the Company's license or collaboration agreements that are within the scope of ASC 606. The Company's contracts with customers typically include promises related to licenses to intellectual property and research and development services. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenue from non-refundable, up-front fees allocated to the license when the license is transferred to the licensee and the licensee is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgement to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and if, over time, the appropriate method of measuring progress for purposes of recognizing revenue from non-refundable, up-front fees. The Company's contracts may include options to acquire additional goods and/or services.

The terms of the Company's arrangements with customers typically include the payment of one or more of the following: (i) non-refundable, up-front payment, (ii) development, regulatory and commercial milestone payments, (iii) future options and (iv) royalties on net sales of licensed products. Accordingly, the transaction price is generally comprised of a fixed fee due at contract inception and variable consideration in the form of milestone payments due upon the achievement of specified events and tiered royalties earned when customers recognize net sales of licensed products. The Company measures the transaction price based on the amount of consideration to which it expects to be entitled in exchange for transferring the promised goods and/or services to the customer. The Company utilizes the "most likely amount" method to estimate the amount of variable consideration, to predict the amount of consideration to which it will be entitled for its one open contract. Amounts of variable consideration are included in the transaction price to the extent that it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved. Milestone payments that are not within the control of the Company or the licensee, such as those dependent upon receipt of regulatory approval, are not considered to be probable of achievement until the triggering event occurs. At the end of each reporting period, the Company reevaluates the probability of achievement of each milestone and any related constraint, and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenue and net loss in the period of adjustment.

For arrangements that include sales-based royalties, including milestone payments based upon the achievement of a certain level of product sales, the Company recognizes revenue upon the later of: (i) when the related sales occur or (ii) when the performance obligation to which some or all of the payment has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any development, regulatory or commercial milestones or royalty revenue resulting from any of its collaboration arrangements. Consideration that would be received for optional goods and/or services is excluded from the transaction price at contract inception.

The Company allocates the transaction price to each performance obligation identified in the contract on a relative standalone selling price basis, when applicable. However, certain components of variable consideration are allocated specifically to one or more particular performance obligations in a contact to the extent both of the following criteria are met: (i) the terms of the payment relate specifically to the efforts to satisfy the performance obligation or transfer the distinct good or service and (ii) allocating the variable amount of consideration entirely to the performance obligation or the distinct good or service is consistent with the allocation objective of the standard whereby the amount allocated depicts the amount of consideration to which the entity expects to be entitled in exchange for transferring the promised goods or services. The Company develops assumptions that require judgement to determine the standalone selling price for each performance obligation identified in each contract. The key assumptions utilized in determining the standalone selling price for each performance obligation may include forecasted revenues, development timelines, estimated research and development costs, discount rates, likelihood of exercise and probabilities of technical and regulatory success.

Revenue is recognized based on the amount of the transaction price that is allocated to each respective performance obligation when or as the performance obligation is satisfied by transferring a promised good and/or service to the customer. For performance obligations that are satisfied over time, the Company recognizes revenue by measuring the progress toward complete satisfaction of the performance obligation using a single method of measuring progress which depicts the performance in transferring control of the associated goods and/or services to the customer. The Company uses input methods to measure the progress toward the complete satisfaction of performance obligations satisfied over time. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenue and net loss in the period of adjustment. The Company measures progress toward satisfaction of the performance obligation over time as effort is expended.

Collaboration Agreement with Merck

On November 14, 2017, the Company entered into a collaboration agreement (the "Merck Collaboration Agreement") with Merck Sharp & Dohme Corp. ("Merck") for a partnership to research and develop certain of the Company's proprietary biologics that target certain autoimmune disease indications (the "Initial Indications"). The Company viewed the Merck Collaboration Agreement as a component of its development strategy since it allowed the Company to advance its autoimmune programs in partnership with a world class pharmaceutical company, while allowing its continued focus on its more advanced cancer programs. The research program outlined in the Merck Collaboration Agreement entailed (1) the Company's research, discovery and development of certain Immuno-STAT™ drug product candidates up to the point of demonstration of certain biologically relevant effects ("Proof of Mechanism") and (2) the further development by Merck of the Immuno-STAT drug product candidates that have demonstrated Proof of Mechanism (the "Proposed Product Candidates") up to the point of demonstration of all or substantially all of the properties outlined in such Proposed Product Candidates' profiles as described in the Merck Collaboration Agreement. The research collaboration term under the Merck Collaboration Agreement expired on December 31, 2021 and, as of December 20, 2022, the Merck Collaboration Agreement terminated. Because the Company has determined to prioritize and strategically focus on its CUE-101 and CUE-102 oncology programs in its IL-2 based CUE-100 series, the Company is not currently pursuing further development of these Immuno-STAT drug product candidates at this time.

In exchange for the licenses and other rights granted to Merck under the Merck Collaboration Agreement, Merck paid to the Company a $2.5 million nonrefundable up-front payment. The Merck Collaboration Agreement required the Company to use the first $2.5 million of milestone payments it received under the agreement to fund contract research.

As it relates to the Merck Collaboration Agreement, the Company recognized the up-front payment associated with its one open contract as a contract liability upon receipt of payment as it requires deferral of revenue recognition to a future period until the Company performed its obligations under the arrangement. Amounts expected to be recognized as revenue within the twelve months following the balance sheet date are classified in current liabilities. Amounts not expected to be recognized as revenue within the twelve months following the balance sheet date are classified as contract liabilities, net of current portion. The Company determined that there was one performance obligation, consisting of the license and research development services. Thus, the transaction price of $2.5 million was allocated to the single performance obligation.

Aside from the $2.8 million in milestone payments earned to date, the Company does not believe that any variable consideration should be included in the transaction price at December 31, 2022. The Company's assessment ensured that estimates of variable consideration would be included in the transaction price only to the extent the Company had a high degree of confidence that revenue would not be reversed in a subsequent reporting period. For the years ended December 31, 2022 and 2021, the Company recorded approximately $0 and $2,155,000, respectively, in collaboration revenue related to the Merck

Collaboration Agreement. The Company did not record short or long-term research and development liabilities on its balance sheet dated December 31, 2022 and December 31, 2021, as the performance obligation was completed on December 31, 2021. The research term and financial support of research conducted under the Merck Collaboration Agreement expired on December 31, 2021, and as of December 20, 2022, all rights granted to Merck under the Merck Collaboration Agreement were returned to us with no further obligations to Merck.

Collaboration Agreement with LG Chem

On November 6, 2018, the Company entered into a collaboration agreement (the "LG Chem Collaboration Agreement") with LG Chem Ltd. ("LG Chem") related to the development of the Company's Immuno-STATs focused in the field of oncology. Pursuant to the LG Chem Collaboration Agreement, the Company granted LG Chem an exclusive license to develop, manufacture and commercialize the Company's lead product, CUE-101, as well as Immuno-STATs that target T cells against two additional cancer antigens, in certain Asian countries (collectively, the "LG Chem Territory"). On April 30, 2021, LG Chem's option pursuant to the Global License and Collaboration Agreement entered into between the Company and LG Chem on December 18, 2019 and as amended on November 5, 2020 (the "Global License and Collaboration Agreement"), expired, and accordingly the Company no longer has any material obligations under the Global License and Collaboration Agreement. In June 2021, after ongoing discussions regarding the selection of the second of the two additional cancer antigens, LG Chem and the Company agreed to let the selection period expire without a second antigen being selected. The Company retains rights to develop and commercialize all assets included in the LG Chem Collaboration Agreement in the United States and in global markets outside of the LG Chem Territory. In exchange for the licenses and other rights granted to LG Chem under the LG Chem Collaboration Agreement, LG Chem made a $5.0 million equity investment in common stock of the Company and a $5.0 million nonrefundable up-front cash payment. The Company is also eligible to receive up to an additional $400.0 million in research, development, regulatory and sales milestones. In addition, the LG Chem Collaboration Agreement also provides that LG Chem will pay the Company tiered single-digit percentage royalties on net sales of commercialized drug product candidates in the LG Chem Territory.

On May 16, 2019, LG Chem paid the Company a $2.5 million milestone payment for the U.S. Food and Drug Administration's ("FDA") acceptance of the investigational new drug application ("IND") for the Company's lead drug product candidate, CUE-101, pursuant to the LG Chem Collaboration Agreement. The $2.5 million milestone payment was recorded as a contract liability upon receipt of payment as it requires deferral of revenue recognition to a future period until the Company performs its obligations under the arrangement. Of the $2.5 million milestone payment, approximately $412,500 was recognized as tax withholding, shown as income tax expense on the consolidated statement of operations and other comprehensive loss.

On December 7, 2020, the Company earned a $1.25 million milestone payment on the selection of a pre-clinical candidate pursuant to the LG Chem Collaboration Agreement. The $1.25 million milestone payment was recorded as a contract liability upon receipt. Revenue related to this milestone payment will be recognized by the Company pursuant to the Company's revenue recognition policy in relation to the performance of its obligations related to the development of this pre-clinical candidate. Of the $1.25 million milestone payment, approximately $206,250 was withheld as payment of foreign tax withholding and shown as income tax expense on the consolidated statement of operations and other comprehensive loss.

On November 23, 2021 the Company earned a $3 million milestone payment for the selection of a clinical product candidate in partnership with LG Chem. The $3 million milestone payment was recorded as a contract liability upon receipt. Revenue related to this milestone payment will be recognized by the Company pursuant to the Company's revenue recognition policy in relation to the performance of its obligations related to the development of this preclinical candidate. Of the $3 million milestone payment, approximately $495,000 was withheld as payment of foreign tax withholding and shown as income tax expense on the consolidated statements of operations and comprehensive loss. Cash was collected in relation to this milestone payment in February 2022.

Aside from the $6.75 million in milestone payments earned to date, the Company does not believe that any variable consideration should be included in the transaction price as of December 31, 2022. Such assessment considered the application of the constraint to ensure that estimates of variable consideration would be included in the transaction price only to the extent the Company had a high degree of confidence that revenue would not be reversed in a subsequent reporting period. The Company will re-evaluate the transaction price, including the estimated variable consideration included in the transaction price and all constrained amounts, in each reporting period and as other changes in circumstances occur. For the years ended December 31, 2022 and 2021, the Company recognized revenue of approximately $1,245,000 and approximately $12,786,000, respectively, related to the LG Chem Collaboration Agreement. The Company did not record short or long-term research and development liabilities on its balance sheet dated December 31, 2022, as the performance obligation was met and completed. As of December 31, 2021, the Company recorded short- and long-term research and development liabilities on its balance

sheet of approximately $645,000. Research and development cost sharing provisions under the agreement expired on March 31, 2022.

Capitalization of Contract Costs

The Company considered the capitalization of contract costs under the guidance in ASC 340-40, *Other Assets and Deferred Costs: Contracts with Customers*. There were no contract costs identified in the Merck Collaboration Agreement. As it related to the LG Chem Collaboration Agreement, the Company capitalized license expenses of approximately $908,000 as of December 31, 2022, paid to Einstein pursuant to the Einstein License Agreement which requires the Company to pay a percentage of sublicenses related to the Company's patent rights for components of its core technology that is licensed from Einstein. This amount is comprised of approximately $438,000 of capitalized license expenses related to the up-front payment received from LG Chem in December 2018, approximately $313,000 in capitalized license expenses related to the milestone payment received in June 2019, and approximately $157,000 in capitalized license expenses related to the milestone payment received in December 2020, net of accumulated amortization of approximately $908,000. As of December 31, 2022, no capitalized license expenses net of accumulated amortization were included in prepaid expenses and other short-term assets related to the LG Chem Collaboration Agreement. As of December 31, 2021, $80,000 was included in prepaid expenses and other short-term assets.

12. Stockholders' Equity

Preferred Stock

The Company has authorized a total of 10,000,000 shares of preferred stock, par value $0.001 per share, none of which were outstanding at December 31, 2022 and 2021. The Company's Board of Directors has the authority to issue preferred stock and to determine the rights, preferences, privileges, and restrictions, including voting rights.

Common Stock

The Company has authorized a total of 100,000,000 shares of common stock, par value $0.001 per share, of which 43,042,548 shares and 32,202,496 shares were issued and outstanding at December 31, 2022 and 2021, respectively.

Warrants

Information with respect to warrants and Pre-Funded Warrants issued is described in Note 10.

13. Related Party Transactions

Information with respect to payments under the Einstein License is described in Note 8.

14. Income Taxes

The Company accounts for income taxes under the provision of ASC 740, Income Taxes. The Company did not report a tax provision for the year ended December 31, 2022 due to historical carryforward net operating losses. The Company reported a $495,000 tax provision for the year ended December 31, 2021 related to foreign withholding taxes paid.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of the Company's deferred tax assets as of December 31, 2022 and 2021 are as follows:

	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 49,708,000	$ 45,994,000
Research and other credits	5,841,000	3,708,000
R&D Capitalization	8,183,000	—
Reserves and accruals	8,574,000	7,552,000
Other	291,000	301,000
Total gross deferred tax assets	72,597,000	57,555,000
Less valuation allowance	(70,010,000)	(54,782,000)
Total deferred tax assets	2,587,000	2,773,000
Deferred tax liability:		
Depreciation	(2,587,000)	(2,773,000)
Other	—	—
Net deferred tax assets	$ —	$ —

In assessing the potential realization of deferred tax assets, management considers whether it is more likely than not that some portion or all of the deferred tax assets will be realized. The ultimate realization of deferred tax assets is dependent upon the Company attaining future taxable income during the periods in which those temporary differences become deductible. As of December 31, 2022 and 2021, management was unable to determine if it is more likely than not that the Company's deferred tax assets will be realized and has therefore recorded a 100% valuation allowance against deferred tax assets at such dates.

No Federal tax provision has been provided for the years ended December 31, 2022 and 2021 due to the losses incurred during such periods. A reconciliation of the difference between the income tax rate computed by applying the U.S. federal statutory rate and the effective tax rate for the years ended December 31, 2022 and 2021 is as follows:

	Years Ended December 31,	
	2022	2021
U. S. federal statutory tax rate	(21)%	(21)%
State taxes	(6)%	(6)%
Change in valuation allowance	29%	29%
Tax credits	(4)%	(3)%
Stock based compensation	1%	1%
Foreign withholding taxes	0%	1%
Other	1%	0%
Effective tax rate	0%	1%

The Company has applied the provisions of ASC 740, which clarifies the accounting for uncertainty in tax positions and requires the recognition of the impact of a tax position in the financial statements if that position is more likely than not of being sustained on a tax return, based on the technical merits of the position, upon examination by the relevant taxing authority. At December 31, 2022 and 2021, the Company had unrecognized tax benefits related to Federal and state research tax credits of approximately $2,491,000 and $2,068,000, respectively. The Company is subject to Federal and state income tax examinations by tax authorities for all years since its incorporation in 2014. The Company is currently not under examination by any tax authority.

At December 31, 2022, the Company has available net operating loss carryforwards for Federal and state income tax purposes of approximately $182,600,000 and $180,300,000, respectively, which, if not utilized earlier, will begin to expire in 2035. Approximately $154.1 million of the federal net operating losses have an indefinite carryforward. The Company has Federal research credits of approximately $6.6 million, which, if not utilized earlier, will begin to expire in 2035, and state research credits of approximately $2.0 million, which, if not utilized earlier, will begin to expire in 2031. Approximately $0.1 million of the state research credits have an indefinite carryforward.

The following is a reconciliation of the Company's gross uncertain tax position at December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
Balance at the beginning of year	$ 2,068,000	$ 1,675,000
Additions for current year tax provisions	401,000	363,000
Additions for prior year tax provisions	58,000	30,000
Reductions of prior year tax provisions	(36,000)	—
Balance as of end of year	$ 2,491,000	$ 2,068,000

15. Commitments and Contingencies

Einstein License Agreement

In 2015, the Company entered into the Einstein License Agreement with Einstein for certain patent rights relating to the Company's core technology platform for the engineering of biologics to control T cell activity, precision, immune-modulatory drug product candidates, and two supporting technologies that enable the discovery of costimulatory signaling molecules (ligands) and T cell targeting peptides. The Company entered into an amended and restated license agreement on July 31, 2017, as amended on October 2018, which modified certain obligations of the parties under the Einstein License Agreement. For the years ended December 31, 2022 and 2021, the Company incurred approximately $0 and $619,000, respectively, in fees and to Einstein in relation to this license.

The Company's remaining commitments with respect to the Einstein License are based on the attainment of future milestones. The aggregate amount of milestone payments made under the Einstein License may equal up to $1.85 million for each Licensed Product, and up to $1.85 million for each new indication of a Licensed Product. Additionally, the aggregate amount of one-time milestone payments based on cumulative sales of all Licensed Products may equal up to $5.75 million. The Company is also party to a service agreement with Einstein to support the Company's ongoing research and development activities.

Collaboration Agreement with Merck

See discussion of the Merck Collaboration Agreement in Note 11.

Collaboration Agreement with LG Chem

See discussion of the LG Chem Collaboration Agreement in Note 11.

Contingencies

The Company accrues for contingent liabilities to the extent that the liability is probable and estimable. There are no accruals for contingent liabilities in these consolidated financial statements.

The Company may be subject to various legal proceedings from time to time as part of its business. As of December 31, 2022, the Company was not a party to any legal proceedings or threatened legal proceedings, the adverse outcome of which, individually or in the aggregate, would have a material adverse effect on its business, financial condition or results of operations.

16. Leases

On March 28, 2022, the Company entered into a License Agreement (the “License”) with MIL 40G, LLC (the “Licensor”), pursuant to which the Company leases approximately 13,000 square feet of office, research and development and laboratory space located at 40 Guest Street, Boston, Massachusetts 02135 (the “Premises”). The Company relocated its corporate headquarters to the Premises in April 2022. On March 28, 2022, the Company terminated its office and lab space lease in Cambridge Massachusetts (the "Laboratory and Office Lease") effective April 30, 2022. The Company performed an analysis of the accounting implications of this termination based on ASC 360 Impairments and Abandonments guidance. For the year ended December 31, 2022, the Company recorded an adjustment to decrease the right-of-use asset and lease liability of approximately $8,124,000 and $8,382,000, respectively, and recorded a gain on right-of-use asset included in the consolidated statement of operations and comprehensive loss of approximately $258,000.

The Company recognized a right of use asset of approximately $9,056,000 and an operating lease liability of approximately $9,056,000 which were recorded as of the Term Commencement Date (as defined below) related to the License.

The term of the License commenced on April 15, 2022 (the “Term Commencement Date”) and expires on April 14, 2026 (the “Term”). The License has a monthly rental rate of $200,700 for the first year of the Term, $208,728 for the second year of the Term, $217,077 for the third year of the Term and $225,760 for the remainder of the Term. Pursuant to the License, the Company prepaid two months of rent and a security deposit. The Licensor is obligated under the License to provide certain services to the Company, including providing certain gases, chemicals and equipment to the Premises’ laboratory space, IT support, security, office support and health and safety training. The Licensor has the right to terminate the License for Cause (as defined in the License).

On May 3, 2022, the Company entered into the First Amendment to the License ("First Amendment”) with the Licensor, pursuant to which the License was expanded to include an additional room effective July 15, 2022. In consideration of the First Amendment, the security deposit was increased from $225,760 to $235,884 effective July 15, 2022. Upon execution of the First Amendment, the Company prepaid three months of rent, two of which will be held in escrow and credited against future rent payments and the other of which was applied to the first month’s rent. Effective July 15, 2022, the monthly rental rate under the First Amendment increased to $209,700 from $200,700. During the year ended December 31, 2022, the Company recognized a right of use asset of approximately $369,000 and a short and long term operating lease liability of approximately $100,300 and $260,600, respectively, using the weighted average discount rate of 8%, which were recorded as of the Term Commencement Date related to the License.

On May 31, 2022, the Company entered into an operating lease for additional laboratory space at 40 Guest Street, Boston, Massachusetts for the period from December 1, 2022, through December 1, 2024 (the “40G Additional Laboratory Lease”). The 40G Additional Laboratory Lease contains escalating payments during the lease period. The monthly rental rate under the 40G Additional Laboratory Lease is $59,152 for the first 12 months and $61,519 for the remainder of the term. Under the terms of this lease agreement, the Company prepaid three months of rent, two of which are held in escrow and will be credited against future rent payments and the other of which was applied to the first month’s rent. During the year ended December 31, 2022, the Company recognized a right of use asset of approximately $1,307,000 and a short and long term operating lease liability of approximately $712,000, and $535,000, respectively, using the weighted average discount rate of 10%, which were recorded as of the Term Commencement Date related to the License.

On September 9, 2022, the Company terminated its lab space lease in Cambridge, Massachusetts with MIL 21E, LLC with an effective termination date of December 6, 2022. The Company performed an analysis of the accounting implications of this termination based on ASC 360 Impairments and Abandonments guidance. During the year ended December 31, 2022, the Company recorded an entry to remove the remaining lease liability and right of use asset of $963,000 and $945,000, respectively. The difference between the carrying amounts of the right of use asset and lease liability of $19,000 was recorded to gain on right of use asset and included in the consolidated statement of operations and comprehensive loss.

For the year ended December 31, 2022, the Company recorded approximately $626,000 in interest expense to the lease liability.

At December 31, 2022, the Company recorded approximately $9,203,000 to operating lease right-of-use asset, and approximately $3,300,000 and $6,018,000 to the short-term and long-term operating lease liability, respectively. At December 31, 2021, the Company recorded approximately $9,809,876 to operating lease right-of-use asset, and approximately $4,931,675 and $5,121,179 to short- and long-term operating lease liability, respectively. As of December 31, 2022 and 2021, a security deposit of approximately $794,000 was included in deposits on the Company’s consolidated balance sheet related to the 40G

Additional Laboratory Lease. Cash was collected in the amount of approximately $803,000 for the 21 Erie Laboratory and Office Lease during the year ended December 31, 2022. At December 31, 2022, the remaining lease term was 3.29 years.

Future minimum lease payments under these leases at December 31, 2022 are as follows:

Year	
2023	$ 3,300,174
2024	3,368,201
2025	2,799,157
2026	818,069
Total lease payments	10,285,601
Less: present value discount	(967,815)
Present value of lease payments	$ 9,317,786

Total rent expense of approximately $4,182,000 and $4,963,000 was included in the consolidated statements of operations and comprehensive loss for the years ended December 31, 2022 and 2021, respectively.

17. Cue Biopharma 401(k) Plan

Effective as of January 1, 2017, the Company adopted the Cue Biopharma 401(k) Plan (the “Plan”) for all employees of the Company. Employees may participate in the Plan upon complying with the Plan’s eligibility requirements, subject to limitations imposed by the Internal Revenue Service. Under the Plan, the Company may match employee contributions at its discretion. The Company made contributions of approximately $245,000 and $0 to the Plan during the years ended December 31, 2022 or 2021, respectively.

18. Subsequent Events

On February 22, 2023, the Company entered into a strategic collaboration with Ono Pharmaceutical Co., Ltd. ("Ono") to further develop CUE-401 and provide dedicated resources and capabilities to help advance CUE-401 toward the clinic. Under the terms of the agreement, Ono will pay Cue Biopharma an upfront payment and fully fund all research activities related to CUE-401 through a specified option period. During this option period, Cue Biopharma will be responsible for the research and development of CUE-401. Upon Ono’s exercise of its option to license CUE-401, Cue Biopharma will receive an option exercise payment and be eligible for development and commercial milestone payments up to an aggregate of approximately $220 million, as well as tiered royalties on sales. Upon any such exercise, Ono will receive worldwide rights to develop and commercialize CUE-401, with the Company retaining a 50% co-development and co-commercialization right in the United States.

Silicon Valley Bank (“SVB”) was closed on March 10, 2023 by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation (“FDIC”) as receiver. At the time of closing, the Company maintained approximately 20% of its cash and cash equivalents in deposit accounts with SVB. The vast majority of the Company’s cash, cash equivalents and marketable securities reside in custodial accounts at US Bank for which SVB Asset Management is the advisor. The Company’s investment portfolio currently does not contain any securities of SVB. The FDIC has reopened SVB as Silicon Valley Bridge Bank, N.A. (“SVBB”). SVBB continues to hold the Company’s Term Loans as well as deposit and sweep accounts under the existing terms and covenants which were in place at SVB prior to the receivership.

PART IV

Item 15. Exhibit and Financial Statement Schedules

(a) List of documents filed as part of this report:

1. Financial Statements (see "Financial Statements and Supplementary Data" at Item 8 and incorporated herein by reference).

2. Financial Statement Schedules (Schedules to the Financial Statements have been omitted because the information required to be set forth therein is not applicable or is shown in the accompanying Financial Statements or notes thereto)

3. Exhibits

The following is a list of exhibits filed as part of this Annual Report on Form 10-K:

Exhibit Number	Exhibit Description	Incorporated by Reference				
		Filed Herewith	Form	Exhibit	Filing Date	Registration /File No.
3.1	Amended and Restated Certificate of Incorporation of the Registrant, as amended		10-Q	3.1	11/09/20	001-38327
3.2	Amended and Restated Bylaws of the Registrant		S-1	3.5	12/05/17	333-220550
4.1	Specimen Certificate representing shares of common stock of the Registrant		S-1	4.1	12/05/17	333-220550
4.2	Description of Common Stock of the Registrant Registered Pursuant to Section 12 of the Securities Exchange Act of 1934		10-K	4.4	03/12/2020	001-38327
4.3	Form of Pre-Funded Warrant to Purchase Common Stock		8-K	4.1	11/15/2022	001-38327
4.4	Form of Warrant to Purchase Common Stock or Pre-Funded Warrant		8-K	4.2	11/15/2022	001-38327
10.1	Form of Registration Rights Agreement between the Registrant and investors for an offering completed on June 15, 2015		S-1	10.4	09/21/17	333-220550
10.2	Form of Joinder and Amendment to Registration Rights Agreement between the Registrant and investors for an offering completed on December 22, 2016		S-1	10.6	09/21/17	333-220550
10.3#	First Amendment to Collaboration, License and Option Agreement, dated March 15, 2019, between the Registrant and LG CHEM LTD.		10-K	10.3	03/09/21	001-38327
10.4#	Second Amendment to Collaboration, License and Option Agreement, dated August 5, 2019, between the Registrant and LG CHEM LTD.		10-K	10.4	03/09/21	001-38327
10.5#	Third Amendment to Collaboration, License and Option Agreement, dated October 29, 2019, between the Registrant and LG CHEM LTD.		10-K	10.5	03/09/21	001-38327
10.6#	Fourth Amendment to Collaboration, License and Option Agreement, dated December 18, 2019, between the Registrant and LG CHEM LTD.		10-K	10.6	03/09/21	001-38327

10.7#	Fifth Amendment to Collaboration, License and Option Agreement, dated January 10, 2020, between the Registrant and LG CHEM LTD.		10-K	10.7	03/09/21	001-38327
10.8#	Sixth Amendment to Collaboration, License and Option Agreement, dated February 14, 2020, between the Registrant and LG CHEM LTD.		10-K	10.8	03/09/21	001-38327
10.9#	Seventh Amendment to Collaboration, License and Option Agreement, dated May 14, 2020, between the Registrant and LG CHEM LTD.		10-K	10.9	03/09/21	001-38327
10.10#	Eighth Amendment to Collaboration, License and Option Agreement, dated December 7, 2020, between the Registrant and LG CHEM LTD.		10-K	10.10	03/09/21	001-38327
10.11	Form of Indemnification Agreement between the Registrant and its directors and officers	X				
10.12†	Amended and Restated License Agreement by and between the Registrant and Albert Einstein College of Medicine dated July 31, 2017		S-1	10.11	12/13/17	333-220550
10.13*	Cue Biopharma, Inc. 2016 Omnibus Incentive Plan, as amended and restated		S-1	10.13	09/21/17	333-220550
10.14*	Form of stock option award under 2016 Omnibus Incentive Plan		S-1	10.14	09/21/17	333-220550
10.15*	Cue Biopharma, Inc. 2016 Non-Employee Equity Incentive Plan		S-1	10.15	09/21/17	333-220550
10.16*	Form of stock option award under 2016 Non-Employee Equity Incentive Plan		S-1	10.16	09/21/17	333-220550
10.17*	Director Compensation Policy dated January 1, 2021		10-Q	10.3	05/10/2022	001-38327
10.18†	Exclusive Patent License and Research Collaboration Agreement between the Registrant and Merck Sharp & Dohme Corp. dated November 14, 2017		S-1	10.21	12/04/17	333-220550
10.19*	Executive Employment Agreement between the Registrant and Colin G. Sandercock dated as of November 15, 2017		S-1	10.22	12/04/17	333-220550
10.20†	Collaboration, License and Option Agreement between the Registrant and LG Chem, Ltd. dated November 6, 2018		8-K	10.1	12/26/18	001-38327
10.21*	Amendment No. 1 to Cue Biopharma, Inc. 2016 Omnibus Incentive Plan		10-K	10.16	03/12/2020	001-38327
10.22*	Amended and Restated Executive Employment Agreement between the Registrant and Anish Suri dated October 3, 2019		8-K	10.1	10/07/19	001-38327
10.23	Third Amended and Restated Executive Employment Agreement dated March 4, 2021 between the Company and Daniel Passeri		10-K	10.26	03/09/21	001-38327
10.24	Executive Employment Agreement dated August 21, 2020 between Registrant and Kerri-Ann Millar		8-K	10.1	08/24/20	001-38327
10.25#	First Amendment to the Exclusive Patent License and Research Collaboration Agreement with Merck Sharp & Dohme Corp. dated November 9, 2020		10-K	10.28	03/09/21	001-38327

10.26	First Amendment to the Amended and Restated License Agreement with Albert Einstein College of Medicine dated October 30, 2018		10-K	10.30	03/09/21	001-38327
10.27	Open Market Sale Agreement[SM], dated October 1, 2021, by and between Cue Biopharma, Inc. and Jefferies LLC		10-Q	10.1	11/09/21	001-38327
10.28#	Loan and Security Agreement, dated February 15, 2022, by and between Cue Biopharma, Inc. and Silicon Valley Bank		10-K	10.34	03/16/2022	001-38327
10.29	License Agreement, dated March 28, 2022, between Cue Biopharma, Inc. and MIL 40G, LLC		8-K	10.1	03/30/2022	001-38327
10.30	First Amendment to the License Agreement, dated May 3, 2022, between Cue Biopharma, Inc. and MIL 40G, LLC		10-Q	10.1	08/04/2022	001-38327
10.31	Rider to License Agreement, dated as of July 7, 2022, between Cue Biopharma, Inc. and MIL 40G, LLC		10-Q	10.2	08/04/2022	001-38327
10.32	Termination of License Agreement, dated September 9, 2022, between Cue Biopharma, Inc. and MIL 21E, LLC		10-Q	10.1	11/14/2022	001-38327
10.33	Form of Securities Purchase Agreement, dated November 14, 2022, by and among the Company and the other parties thereto		8-K	10.1	11/15/2022	001-38327
10.34	Registration Rights Agreement, dated November 14, 2022, by and among the Company and the other parties thereto		8-K	10.2	11/15/2022	001-38327
21.1	List of Subsidiaries	X				
23.1	Consent of RSM US LLP, Independent Registered Public Accounting Firm	X				
24.1	Power of Attorney (included on signature page)	X				
31.1	Certification Pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934	X				
31.2	Certification Pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934	X				
32.1	Certification Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002	X				
101.INS	Inline eXtensible Business Reporting Language (XBRL) Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document	X				
101.SCH	Inline XBRL Taxonomy Extension Schema Document	X				
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document	X				
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document	X				
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document	X				

101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document	X
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101)	X

***** Indicates management compensatory plan, contract or arrangement.
† Confidential treatment has been granted as to portions of this exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.
# Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Cue Biopharma, Inc.

Dated: March 21, 2023

By: /s/ Daniel R. Passeri
Daniel R. Passeri
Chief Executive Officer and Director
(Principal Executive Officer)

POWER OF ATTORNEY AND SIGNATURES

We, the undersigned officers and directors of Cue Biopharma, Inc., hereby severally constitute and appoint Daniel R. Passeri and Kerri-Ann Millar our true and lawful attorney, with full power to him to sign for us and in our names in the capacities indicated below, any amendments to this Annual Report on Form 10-K, and generally to do all things in our names and on our behalf in such capacities to enable Cue Biopharma, Inc. to comply with the provisions of the Securities Exchange Act of 1934, as amended, and all the requirements of the Securities Exchange Commission.

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

Signatures	Title	Date
/s/ Daniel R. Passeri Daniel R. Passeri	Chief Executive Officer and Director (Principal Executive Officer)	March 21, 2023
/s/ Kerri-Ann Millar Kerri-Ann Millar	Chief Financial Officer (Principal Financial and Accounting Officer)	March 21, 2023
/s/ Aaron Fletcher Aaron Fletcher	Director	March 21, 2023
/s/ Peter A. Kiener Peter A. Kiener	Director	March 21, 2023
/s/ Frederick Driscoll Frederick Driscoll	Director	March 21, 2023
/s/ Frank Morich Frank Morich	Director	March 21, 2023
/s/ Tamar Howson Tamar Howson	Director	March 21, 2023

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report, including the CEO's Letter to Cue Biopharma Shareholders, contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, including without limitation any statements with respect to Cue Biopharma's plans, strategies, objectives, prospects or results; statements of belief and expectation concerning research and development, including plans to initiate or continue clinical trials and preclinical studies, timelines, anticipated results, and the therapeutic potential of drug product candidates; statements of assumptions underlying any of the foregoing and other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "potential," "will," "would," "could," "should," "continue," "seek," "strategy," and similar expressions. These forward-looking statements are not guarantees of future performance and involve risks, uncertainties, assumptions and other important factors that may cause actual results to be materially different from those indicated by such forward-looking statements. Factors that may cause or contribute to actual results being materially different from those indicated by forward-looking statements include the factors set forth under the captions "Risk Factor Summary" and "Risk Factors" in the accompanying Annual Report on Form 10-K for the fiscal year ended December 31, 2022 and any subsequent reports filed by Cue Biopharma with the Securities and Exchange Commission. In addition, any forward-looking statements in this Annual Report, including the CEO's Letter to Cue Biopharma Shareholders, represent the views of Cue Biopharma only as of the date of this Annual Report and should not be relied upon as representing Cue Biopharma's views as of any subsequent date. Cue Biopharma disclaims any intention or obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

Corporate Headquarters
40 Guest Street
Boston, Massachusetts 02135

Legal Counsel
WilmerHale
Boston, Massachusetts

Independent Auditors
RSM US LLP
Boston, Massachusetts

Transfer Agent
Computershare
Canton, Massachusetts

Stock Information
The company's common stock is traded on the Nasdaq Capital Market under the symbol CUE.

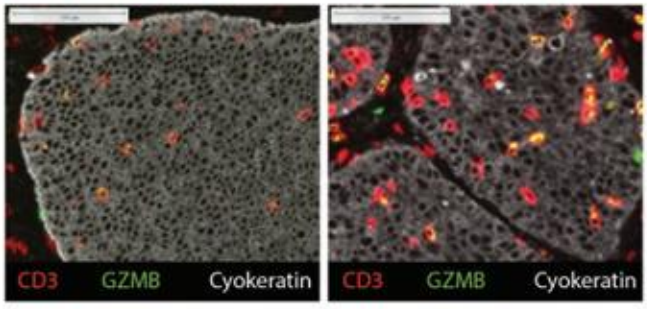
CUE™
BIOPHARMA

www.cuebiopharma.com

Cue Biopharma, Inc.
40 Guest Street
Boston, MA 02135
+1 617-949-2680

NASDAQ: CUE

Pre-CUE-101 Therapy **Post-CUE-101 Therapy**



The two scans above and a portion enlarged on the cover, are pre- and post-CUE-101 treatment biopsies from the same patient, demonstrating an increase in T cell infiltration into tumors and tumor necrosis.