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, 2021

☐ **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.)**
21 Erie Street Cambridge, MA	**02139**
(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. ☐

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 $362.6 million (based on the closing price of the registrant’s common stock on June 30, 2021 of $11.65 per share).

As of March 7, 2022, the registrant had 33,010,702 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, 2021. 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 continuing 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 agreements with Merck and LG Chem contain 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 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

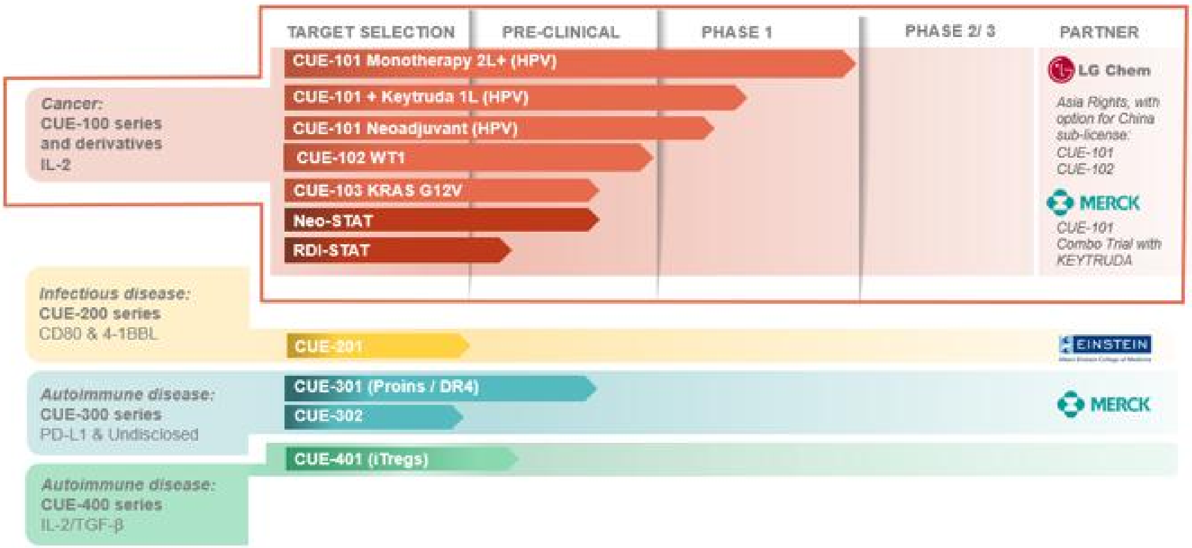
We are a clinical-stage biopharmaceutical company engineering a novel class of injectable biologics to selectively engage and modulate targeted T cells directly within the patient's body. We believe our proprietary Immuno-STAT™ (*Selective Targeting and Alteration of T Cells*) platform, as described 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 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 our 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.

Our Immuno-STAT Platform Pipeline

The pipeline chart below details our current portfolio assets and their stages of development. We have determined to prioritize and strategically focus on our 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 our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series.



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, currently being dosed in a second line and beyond Phase 1b monotherapy trial for human papilloma virus, or HPV, driven recurrent/metastatic head and neck cancer, or R/M HNSCC, as well as in a first line Phase 1 combination trial with KEYTRUDA® (pembrolizumab), the current standard of care, for R/M HNSCC. In June 2021, we completed the dose escalation phase of our monotherapy Phase 1 clinical trial of CUE-101 for the treatment of HPV16-driven R/M HNSCC in late-stage treatment-refractory patients, and subsequently commenced the enrollment expansion stage at the 4mg/kg recommended Phase 2 dose, or RP2D. These patients have received and failed several prior lines of systemic therapy, including checkpoint inhibitors, or CPIs, such as KEYTRUDA, already approved for first-line HPV+R/M HNSCC. To date, CUE-101 has demonstrated a favorable tolerability profile in the monotherapy trial as well as encouraging preliminary anti-tumor clinical activity. In January 2022, we reported that of the 14 evaluable patients dosed at the 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 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 immune stimulation that may result in anti-tumor effects. At the Society for Immunotherapy of Cancer, or SITC, in November 2021, we reported that we have observed preliminary, robust PK with dose proportional exposure that was sustained across repeat dosing with no evidence of drug clearing antibodies.

During the first quarter of 2021, we dosed the first patient in our first-line Phase 1 combination trial of CUE-101 with KEYTRUDA. We believe the potential synergy of CUE-101 with KEYTRUDA is due to their complementary mechanisms of action, specifically, CUE-101's protein engineered design to selectively engage, activate and expand targeted tumor-specific T cells directly in the patient's body and KEYTRUDA's mechanism of checkpoint signaling blockade that prevents the tumor from using PD-1/PDL-1 to shut down attacking T cells.

We believe that CUE-101 has the potential to synergize with and enhance the clinical activity of KEYTRUDA and potentially other CPIs since the presence of expanded tumor-specific T cells is a pre-requisite for and an obligatory target of anti-PD-1 therapy.

As the most advanced candidate from our IL-2 based CUE-100 series, CUE-101 is exemplary of the Immuno-STAT platform and underscores the key immunological targets, or immune activity nodes, required to selectively enhance anti-tumor immunity. 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, and the next-generation platform, Neo-STAT™, as described below).

We are also advancing additional development candidates within the CUE-100 series that we believe have the potential to treat multiple cancers. CUE-102, targets Wilm's tumor protein, or WT1, 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). Preclinical data from CUE-102 were recently presented at the New York Academy of Science Frontiers in Cancer Immunotherapy meeting in May 2021 and at the SITC meeting in November 2021. We believe these data support the premise of selective WT1 specific T cell activation and expansion, along with polyfunctional effector function including killing of target cells. We anticipate filing an investigational new drug application, or IND, for CUE-102 by the end of the first quarter of 2022.

We have also generated foundational preclinical data with Immuno-STATs targeting the mutated G12V KRAS T cell epitope including demonstration of activation and expansion of T cells expressing G12V-specific T cell receptors, or TCRs, and we are developing CUE-103, also in the CUE-100 series, for targeting the KRAS G12V mutation. Preclinical data from CUE-103 were presented at the Immuno-Oncology conference in February 2021 and at the SITC meeting in November 2021.

Importantly, we have expanded the potential reach of the Immuno-STAT platform to address tumor heterogeneity and diversity of many cancers by developing a derivative scaffold from the CUE-100 series containing stable "peptide-less" or "empty" MHC pockets or 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, decreasing time and cost to manufacture and potentially lending itself to personalized neo-antigen strategies in cancer immunotherapy as an off-the-shelf approach. Furthermore, we have attempted to address the resistance mechanism found in a subset of solid tumors which escape immune surveillance by a down-regulation of HLA, thereby making the tumor "invisible" to T cells. Our approach entails a derivative of the CUE-100 series referred to as RDI-STAT taking advantage of the clinical validation of the CUE-100 series from our Immuno-STAT platform, by deploying a targeting moiety on the FC fragment to bind to a surface protein found on the tumor. 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 invoking an immune attack.

We have also developed three additional biologic series within the Immuno-STAT platform outside of oncology: CUE-200, CUE-300, and CUE-400, each specifically designed through rational engineering to possess distinct signaling modules for desired biological mechanisms that may be applied across many diseases. The CUE-200 series is focused on cell surface receptors including CD80 and/or 4-1BBL to address T cell exhaustion associated with chronic infections. The CUE-300 series, for autoimmune diseases, incorporates the inhibitory PD-L1 co-modulator for selective inhibition of the autoreactive T cell repertoire. The CUE-400 series, for autoimmune diseases with diverse or unknown autoantigens, represents a novel class of bispecific molecules designed to selectively and effectively expand induced regulatory T cells, or iTregs. We are actively seeking third party support through partnerships and collaborations, or alternative funding structures, to further develop the CUE-200, CUE-300 and CUE-400 series.

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 IL-2-based CUE-100 series for oncology

- Through CUE-101, as representative and exemplary of our IL-2 based CUE-100 series, we intend to demonstrate that IL-2 can be selectively and tolerably delivered to the specific cellular immune compartment relevant for anti-tumor immunity. These data would be in contrast to other approaches, focused on systemic delivery of IL-2 variants, with little or no specificity for the activation of the anti-tumor T cell repertoire.
- We plan to continue to execute clinical trials that are designed using a translational approach to demonstrate CUE-101’s ability to selectively engage, activate and expand the patients’ own endogenous HPV16-specific T cell repertoire to target, attack and kill tumor cells.
- We plan to expand patient access and potentially enhance clinical outcomes by addressing the significant unmet patient need, which we are currently seeking to do by establishing foundational mechanistic evidence in our second line and beyond monotherapy Phase 1 clinical trial for HPV16-driven R/M HNSCC and in our first-line Phase 1 combination trial with KEYTRUDA in the first-line R/M HNSCC setting.
- Through our ongoing and planned clinical trials, we are working to build a clinical data set that demonstrates the PK/PD, tolerability and anti-tumor effect of CUE-101 as a monotherapy and the potential 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 Immuno-STATs and Neo-STATs with 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 the significant, unmet medical need 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.

Our Approach

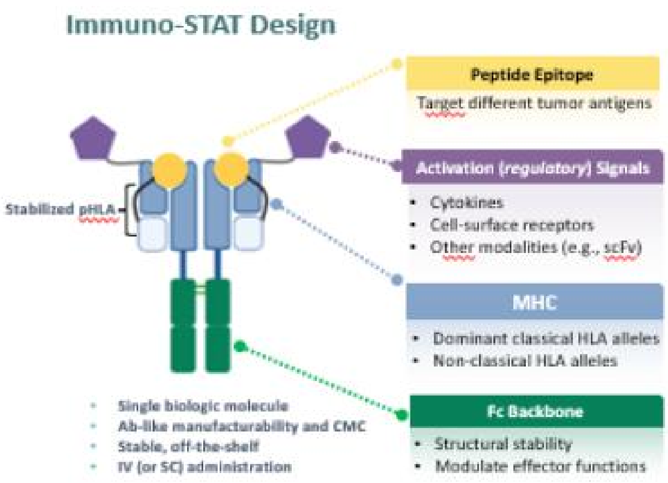
The human immune system is comprised of a number of specialized cell types that collectively function to defend the body against foreign threats as well as the development of cancers. One such specialized cell type, the human T cell, is a subtype of a white blood cell that plays a central role in the 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 pHLA in humans) – that is recognized by the T cell via its 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 damage to the host. 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 (or co-inhibitory) signals.

The core protein framework for the Immuno-STAT platform builds upon our ability to combine the key activation signals for T cell modulation (i.e., Signal 1 and Signal 2) into a singular molecular scaffold. The "activation" of a T cell requires the presence of a distinct co-stimulatory, or co-regulatory signal, including cytokines, such as IL-2. It is important to note that the presence of a "co-stimulatory" signal is essential for effective activation and proliferation.

As shown below, the core framework of an 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, including modified IL-2 in the case of the CUE-100 series, that can be selectively delivered to tumor-specific T cells, representing Signal 2. The core protein framework is built upon an Fc backbone that provides significant structural stability. 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 specific and selective modulation of cancer-relevant T cells while circumventing 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.

Immuno-STAT Platform Framework



***Peptide Epitope & MHC**: A stabilized peptide-major histocompatibility complex (pMHC), Class I or II, to selectively engage disease-relevant T cells by incorporating diverse antigenic peptides of interest and choosing different MHC (or HLA) alleles to provide broad coverage for global patient populations.*

Activation: *Distinct co-stimulatory or co-regulatory signals, including cytokines, cell-surface receptors, and other targeting modalities, to control the activity of disease-relevant T cells.*

Fc Backbone: *Well-characterized protein construct from human antibodies to provide stability and ease of manufacturability that can be engineered to dial in or out biological and effector functions.*

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 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 in February 2022 at the Biophysical Society Annual Meeting supporting the hypothesis that Immuno-STAT's concurrent delivery of antigen and IL-2 signals results in robust synapse formation, providing for selective T cell activation. We believe that the cumulative, preliminary clinical data generated to date in our ongoing Phase 1 trial for CUE-101 supports this underlying hypothesis of selective T cell activation with corresponding antitumor activity and clinical benefit.

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-specifics, 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, we believe that without a bias towards the tumor-specific T cells, via modalities like rIL-2, CPIs or bispecific T cell engagers, will continue to provide sub-optimal outcomes for most patients.

We believe that our IL-2-based CUE-100 series could solve the problem as to how to activate and amplifying only those cancer-relevant immune cells without broadly activating the vast majority of tumor-irrelevant cells, by selectively targeting, activating and proliferating cancer-specific immune cells directly in the patient's body, achieving well tolerated and therapeutically effective dose levels.

We believe that our Immuno-STAT and derivative drug product candidates, such as Neo-STAT, 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 target disease specific T cells with specificity, and selectively 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-specifics;
- Access to a broad set of disease targets and patient populations;
- Standard delivery format (intravenous or subcutaneous) with a convenient dosing schedule (weekly or monthly) for the patient 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.

IL-2 Therapy Challenges

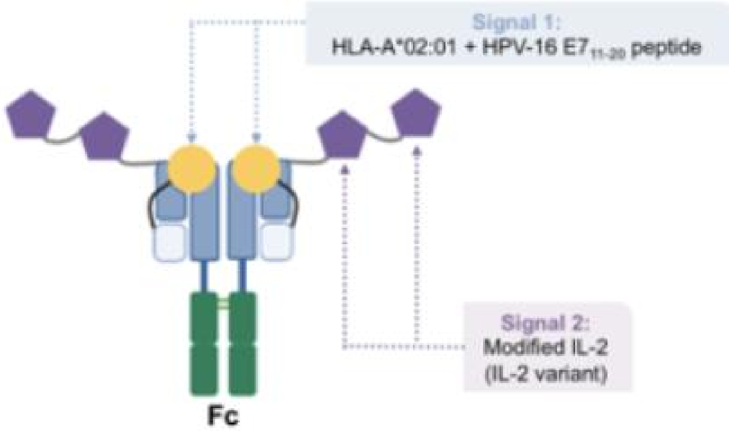
The challenges of current IL-2 therapies have centered around a lack of selectivity and indiscriminate immune activation, resulting in poor tolerability and limited therapeutic dosing ranges. The primary challenge with wild-type IL-2, and the different IL-2 variants in development, is that these molecules will indiscriminately engage the vast majority of the patient's CD8+ T cells, most of which have no relevance to or effect on the patient's tumor.

To maximize the fullest potential of IL-2 for cancer therapy, we engineered 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 only on tumor-specific T cells whose TCR is engaged to 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 HLA-epitope/TCR complex (signal 1) and IL-2 co-stimulatory signaling (signal 2), we believe we are able to enable the selective and specific 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.

<u>CUE-101 Immuno-STAT Design</u>



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 are currently conducting a Phase 1 monotherapy trial of CUE-101 in second line and beyond patients with HPV+R/M HNSCC and a 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 24,600 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 have continued to enroll 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, 38 patients were treated across seven dose-escalation cohorts, ranging from 0.06mg/kg to 8mg/kg, without a maximum tolerated dose having been identified. We believe this demonstrates the specificity and 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 January 2022, we reported that of the 14 evaluable patients dosed at the 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. In January 2022, 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. At SITC, we reported that we have observed preliminary, robust PK with dose proportional exposure that was sustained across repeat dosing with no evidence of 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.

The table below illustrates the safety and tolerability of CUE-101 in the 45 patients treated across all monotherapy doses as of January 25, 2022. As of January 25, 2022, CUE-101 at the RP2D of 4 mg/kg 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.

Preliminary Safety and Tolerability Data from Phase 1 Monotherapy Trial

	Treatment-Related Adverse Events (Monotherapy Treated Subjects N=45)		All Adverse Events (Monotherapy Treated Subjects N=45)	
Preferred Term	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**	**Any Grade**
Overall Frequency	**11 (24.4)**	**33 (73.3)**	**21 (46.7)**	**40 (88.9)**
Fatigue	2 (4.4)	13 (28.9)	2 (4.4)	20 (44.4)
Anaemia	1 (2.2)	2 (4.4)	3 (6.7)	14 (31.1)
Lymphocyte count decreased	3 (6.7)	3 (6.7)	7 (15.6)	12 (26.7)
Chills	0	9 (20.0)	0	11 (24.4)
Hyponatraemia	1 (2.2)	3 (6.7)	1 (2.2)	10 (22.2)
Decreased appetite	0	4 (8.9)	3 (6.7)	9 (20.0)
Weight decreased	0	3 (6.7)	0	9 (20.0)
Infusion related reaction	1 (2.2)	8 (17.8)	1 (2.2)	8 (17.8)
Nausea	1 (2.2)	7 (15.6)	1 (2.2)	8 (17.8)
Cough	0	2 (4.4)	0	7 (15.6)
Dyspnoea	0	1 (2.2)	1 (2.2)	7 (15.6)
Hypophosphataemia	0	4 (8.9)	1 (2.2)	7 (15.6)
Vomiting	2 (4.4)	5 (11.1)	2 (4.4)	7 (15.6)
Arthralgia	0	4 (8.9)	0	6 (13.3)
Blood lactate dehydrogenase increased	0	0	0	6 (13.3)
Blood thyroid stimulating hormone increased	0	3 (6.7)	0	6 (13.3)
Diarrhoea	1 (2.2)	4 (8.9)	1 (2.2)	6 (13.3)

AEs are coded using MedDRA V21.0 and NCICTCAE v5.0. At each level of summation patients reporting > 1 occurrence of the same AE are counted once at highest toxicity.
Treatment-relatedness is assessed by the investigator as 'Definitely', 'Probably', or 'Possibly' related to CUE101.
***Treatment related SAEs (all ≤ 5% frequency):** Anemia, acute kidney injury, dehydration, diarrhea, fatigue, hyponatraemia, infusion-related reaction, nausea, vomiting, rash, syncope, vertigo, (Extracted from EDC 25-JAN-22)*

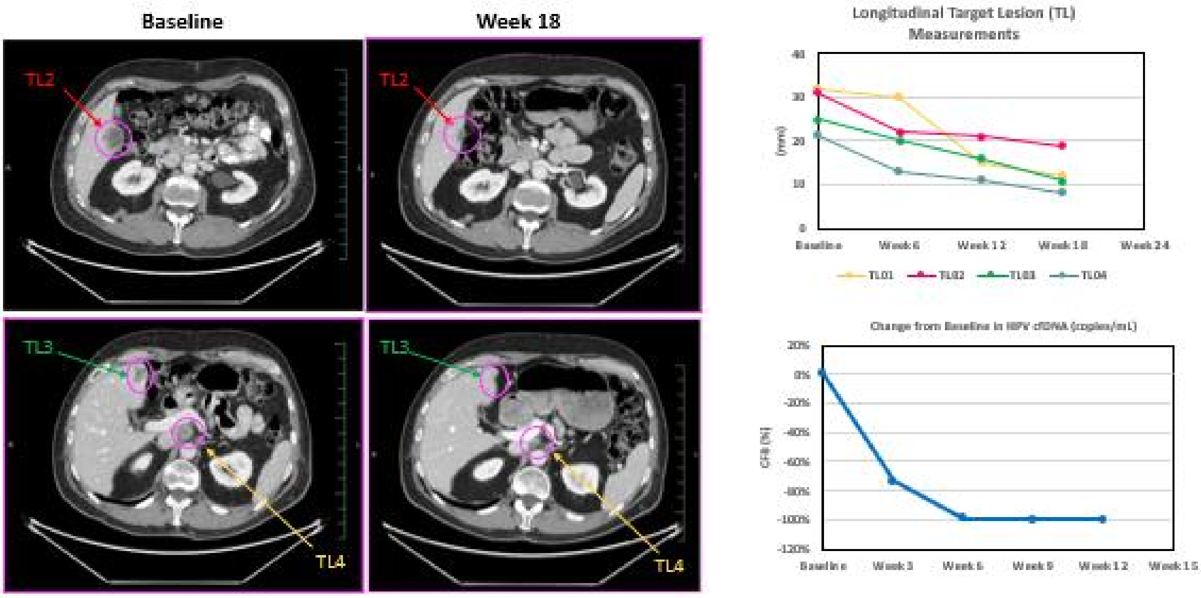
Based on preliminary survival data for the 47 patients treated as of March 13, 2022 with CUE-101 as a monotherapy in both the dose escalation and dose expansion portions of the trial, we estimate median overall survival to be approximately eight months, which approximates the anticipated median overall survival for HPV + HNSCC patients treated with CPIs in the second line setting based on published retrospective analyses. Although preliminary, we are encouraged that as of March 13, 2022, 22 patients remain on treatment or are in follow-up, and we believe this could demonstrate the potential for enhancement of survival in patients treated with CUE-101 as a monotherapy.

Phase 1 Trial of CUE-101 in Combination with KEYTRUDA

During the fourth quarter of 2020, we initiated a Phase 1 clinical trial of CUE-101 in combination with KEYTRUDA in the first-line R/M HNSCC treatment setting. The first patient in this combination study was dosed in the first quarter of 2021. In the third quarter of 2021, we completed the enrollment of the second cohort, at 2 mg/kg, and initiated the enrollment of patients in the third cohort at 4 mg/kg. To date, no dose-limiting toxicities have been observed in the three cohorts. Early signs of activity in the combination study are encouraging, with three of three patients from cohort two, 2 mg/kg, demonstrating reductions in their target tumor lesions on their first scan after two cycles of therapy. To date, of the four patients treated in dose escalation in the second cohort (2mg/kg) and the third cohort (4mg/kg), two patients have ongoing, confirmed partial responses.

As shown in the graphic and charts below, in the patient with a confirmed partial response from cohort 2, reductions were observed in four out of four target lesions.

CUE-101 in Combination Trial Patient Scan Cohort 2



Other Applications of Immuno-STATs to Oncology

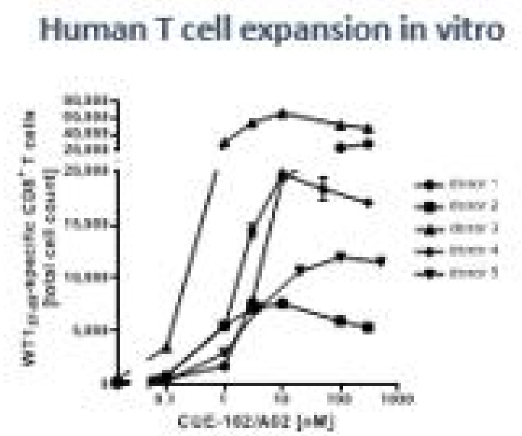
We plan to leverage our Immuno-STAT platform’s modularity and versatility to design and develop additional Immuno-STATs, including CUE-102 and CUE-103, to further address the various therapeutic challenges of cancer, i.e., addressing tumor heterogeneity and escape mechanisms. We have approached this through the flexibility of design 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 HLA-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 across many different cancers to and allows the design of novel constructs incorporating structures having desired combined properties.

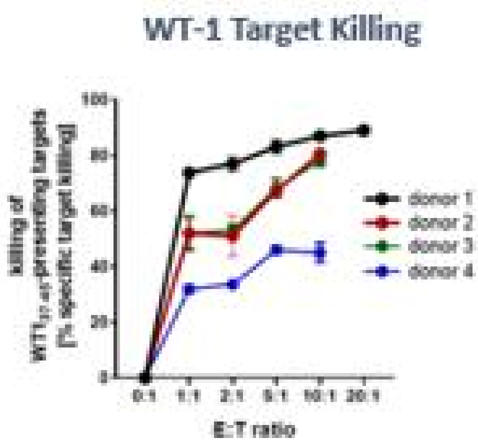
CUE-102

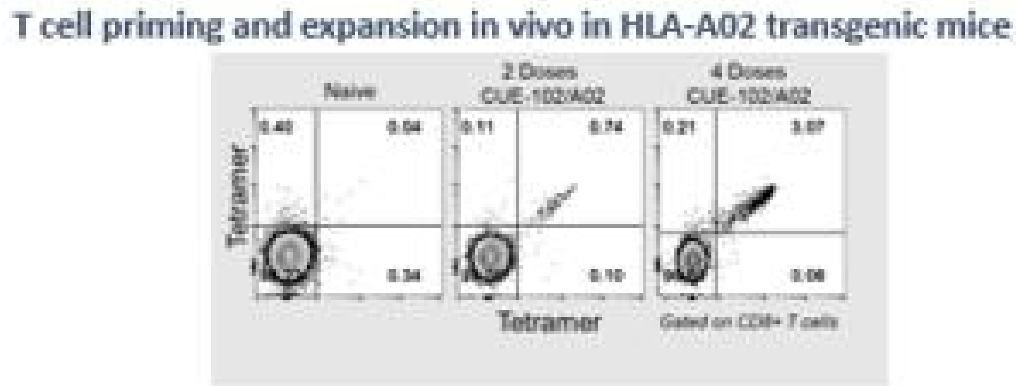
CUE-102 leverages substantially the same CUE-101 framework except the peptide has been changed with a pMHC derived from WT1, an oncofetal antigen known to be over-expressed in more than 20 different cancers, including both solid tumors (such as colorectal, ovarian, pancreatic and lung) and hematologic malignancies (such as acute myeloid leukemia, multiple myeloma and myelodysplastic syndromes). Patients with WT1 associated cancers represent an important unmet clinical need and underscore the opportunity for promising new therapeutics. We anticipate the filing of an IND for CUE-102 by the end of the first quarter of 2022.

We have generated a comprehensive preclinical data set with CUE-102 to support our planned IND filing. We have observed ex-vivo expansion of WT1-specific T cells from primary human donors (as shown in the top left figure below), and in vivo expansion of T cells in HLA-A02 transgenic mice treated with CUE-102 (as shown in the bottom figure before). Importantly, we observed T cells expanded with CUE-102 activating polyfunctionality and cytotoxic killing of target cells (as shown in the top right figure below), both of which are key attributes of a desirable anti-tumor T cell response. Similar to CUE-101, CUE-102 is a fusion protein biologic built on the IL-2 based CUE-100 series designed to target and activate antigen-specific T cells to fight cancers—in the case of CUE-102, those overexpressing WT1.

<u>CUE-102: Expansion and Polyfunctionality of WT1-Specific T Cells</u>







CUE-103

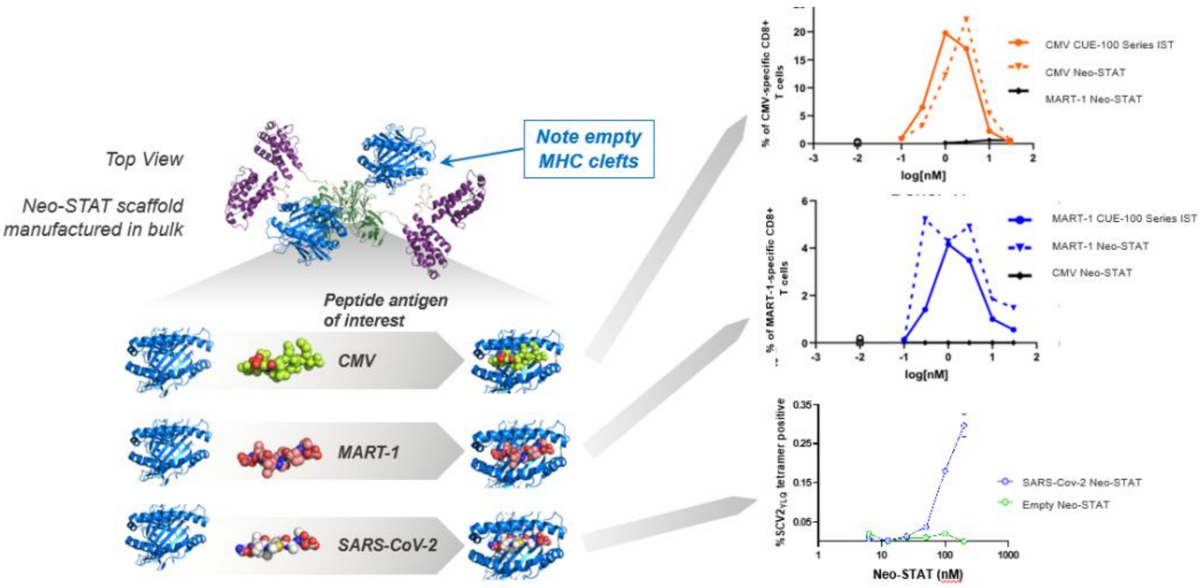
We are also developing CUE-103, a CUE-100 series Immuno-STAT targeting the KRAS G12V mutation. This mutation is associated with many solid tumor types including colorectal carcinoma, lung cancer and pancreatic cancer. We believe the KRAS G12V T cell epitope provides a novel opportunity for immuno-therapeutic targeting of a primary tumor driver mutation, such as KRAS. We disclosed data suggesting the feasibility of production of HLA-A11 Immuno-STATs with functional engagement and activity on targeted T cells possessing T cell receptors specific for the G12V mutation at the SITC meeting in November 2020. These data further underscore the modularity of the Immuno-STAT platform by extending the application to include additional HLA alleles, in this case HLA-A11, as well as modifying the targeting epitope. We are also exploring other HLA alleles, such as A03, to develop additional Immuno-STAT molecules that target KRAS G12V.

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 peptide-conjugation chemistry to covalently attach peptides to the Neo-STAT scaffold. We believe Neo-STAT has the potential to provide enhanced productivities and greater flexibility enabling the ability to generate therapeutic molecules targeting multiple tumor antigens, and to develop future strategies to deploy the Neo-STAT platform for personalized tumor neo-antigens. 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 feasibility proof of concept, 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) or infectious antigens (CMV, SARS-Cov-2), as examples (see below). We presented a detailed description on the protein engineering of the Neo-STAT platform at the Protein Engineering and Cell Therapy Summit meeting in August 2020. We plan to continue to progress the Neo-STAT platform with efforts designed to demonstrate the versatility of our platform approach and the potential for broad therapeutic applications to address the pressing need for more effective cancer immunotherapies. The graphic below illustrates Neo-STATs and Immuno-STATs with the same antigenic peptide activating peptide specific CD8+ T cells.

<u>Neo-STATs and Immuno-STATs with the Same Antigenic Peptide Activate Peptide Specific CD8+ T Cells</u>



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 preclinical studies of CUE-102 targeting T cells recognizing WT1 to address multiple solid and hematological cancers. 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 activities 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 can expand market access and therapeutic reach to patients suffering from a wide range of cancers.

Application of Immuno-STATs Outside of Oncology: CUE-200, 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. In the first instance we have generated data through our collaboration with Merck demonstrating the possibility of a potential clinical candidate with our CUE-300 series 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 activating and increasing 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 iTregs.

Furthermore, we have assessed the potential of developing programs from the Immuno-STAT platform for treating infectious diseases with the CUE-200 series through research being conducted by Dr. Steven Almo, a co-founder of the company and Chair of Biochemistry at The Albert Einstein College of Medicine.

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.

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, 2021, we paid $75,000 to Einstein in license and license maintenance fees under the Einstein License.

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, 2021, we have made one milestone payment of $150,000 for the approval by the FDA of the IND for CUE-101.

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 view this Merck Collaboration Agreement as a component of our development strategy since it will allow 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 entails (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 are elected to be developed by Merck. In addition, so long as Merck continues product development on a Proposed Drug Product Candidate, we are 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 may be 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. Excluding the $2.5 million upfront payment described above, we are 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 are achieved. The Merck Collaboration Agreement requires us to use the first $2.5 million milestone payment we receive under the agreement to fund contract research. The amount of the royalty payments is a percentage of product sales ranging in the single digits based on the amount of such sales.

The term of the Merck Collaboration Agreement extends until the expiration of all royalty obligations following a product candidate's receipt of marketing authorization, at which point Merck's licenses and sublicenses granted under the agreement shall become fully paid-up, perpetual licenses and sublicenses, as applicable. Royalties on each product subject to the Merck Collaboration Agreement shall continue on a country-by-country basis until the expiration of the later of: (1) the last-to-expire patent claiming the compound on which such product is based and (2) a period of ten years after the first commercial sale of such product in such country.

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 the 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 we are discussing with Merck a potential path forward in defining a clinical candidate.

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 U.S. Food and Drug Administration's, or 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, 2021, we recorded approximately $18.3 million in collaboration revenue related to this agreement.

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, 2021, we owned or had licensed seventy-six issued patents, fifty-two pending patent applications in the United States (including eighteen pending U.S. provisional patent applications), twenty pending international PCT applications and 190 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, 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.

Furthermore, immunotherapy technologies are advancing at a rapid pace and we anticipate competing with companies developing bi-specific antibodies attempting to deliver T cell activating cytokines, such as IL-2 (e.g., Amgen Inc., or Amgen, Immunocore Holdings plc, or Immunocore, and Roche Holding AG, or Roche), cell therapies for activating or creating cancer-relevant T cells outside the patient's body, i.e., ex vivo, (e.g., Bristol-Myers Squibb Company, or Bristol-Myers Squibb, Gilead Sciences, Inc., or Gilead, and Novartis AG, or Novartis), antibody-drug conjugates (e.g., Gilead, Roche, Seagen Inc., or Seattle Genetics), immune checkpoint inhibitors (e.g., Bristol-Myers Squibb, Merck, and Pfizer Inc., or Pfizer), and modified cytokines, such as pegylated IL-2 for slower-release (e.g., Bristol-Myers Squibb/Nektar, who in 2020 announced a combination study of BEMPEG plus KEYTRUDA in a Phase 2/3 clinical trial in first-line squamous cell carcinoma of the head and neck), as a means of reducing the unwanted collateral adverse effects of wild type IL-2, genetically-modified IL-2 for ablating the alpha subunit activity to reduce CD4 activation in favor of CD8 (e.g. Neoleukin Therapeutics, Inc., or Neoleukin, Roche, and Sanofi), and antigen-specific targeting of cytokines through nanoparticles (e.g., Neximmune). We believe that our approach provides us with the competitive advantage of antigen-specific targeting of cytokines, such as IL-2 by engineering proteins with a targeting moiety, i.e, peptide-MHC, coupled to genetically modified cytokines, such as not-alpha IL2 for enhancing CD8 activation and attenuated Beta-subunit for biasing the peptide-MHC/TCR affinity, thereby providing cancer antigen specificity.

We expect our lead product candidate, CUE-101, will compete with other product candidates for the treatment of HPV+ cancers. While there is currently no FDA-approved therapy that specifically targets HPV for HPV+ cancers, there are multiple product candidates in clinical development, including cell therapies (e.g., Gilead and Rubius Therapeutics, Inc.), and cancer vaccines (e.g., BioNTech SE, Hookipa Pharma Inc., Inovio Pharmaceuticals, Inc., and ISA B.V.). Therapies not specific to HPV are also being developed to address HPV+ cancers, including immune checkpoint inhibitors as well as tumor infiltrating lymphocytes by Iovance Biotherapeutics, Inc.

Our corporate objective is to design, develop and commercialize new products with superior efficacy, convenience, tolerability, and safety. We expect any drug product candidate that we commercialize, either independently or with our strategic partners, will compete with existing, market-leading products.

There are many companies focused on the development of small molecules and antibodies for cancer treatment. Our core competitors include pharmaceutical and biotechnology organizations, as well as academic research institutions, clinical research laboratories and government agencies that are pursuing research activities in the same therapeutic area. 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 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 guidances. 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. 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 August 2018, the FDA released draft 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.

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, and both NIH and the FDA have recently signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors.

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 law requires the FDA 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. 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 2022 is $3,117,218 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 2022 is $369,413. 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.

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.

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure, and potent and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure, and potent. On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of non-clinical and clinical trial sites to assure compliance with GCPs, the FDA may issue an approval letter or a complete response letter.

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.

- *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.

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. 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.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information.

In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. 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.

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 President Trump 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." It is unclear how this court decision will be implemented by the FDA.

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. 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.

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 2022, the standard fee is $374,858 and the small business fee is $93,714.

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 will become effective in May 2022. The new regulation will replace 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 have until May 2022 to update their Technical Documentation to meet the requirements and comply with the new, more stringent Regulation. Once applicable, 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.

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 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 GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like an 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 U.S., 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 will be 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.

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 the U.S. Department of Health and Human Services, or 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, other healthcare providers 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 have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect, 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.

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 Trump 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, President Biden 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.

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, President Trump 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 implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed by the Biden administration until January 1, 2023.

On July 9, 2021, President Biden 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.

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, 2021, we had 57 full-time employees and two part-time employees. Substantially all of our employees are in Cambridge, 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. 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. During 2020 and 2021, as a result of 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, to the extent those events and meetings are continuing. Many of these protocols remained in place during 2021.

Status as an Emerging Growth Company

We are an "emerging growth company", or EGC, as that term is defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an EGC until December 31, 2022. Section 102(b)(1) of the JOBS Act exempts EGCs from being required to comply with new or revised financial accounting standards until. private companies (*i.e.*, those that have not had a registration statement declared effective under the Securities Act of 1933, as amended, or the Securities Act, or do not have a class of securities registered under the Securities Exchange Act of 1934, as amended, or the Exchange Act) are required to comply with such new or revised financial accounting standards. The JOBS Act also provides that an EGC can elect to opt out of the extended transition period provided by Section 102(b)(1) of the JOBS Act and comply with the requirements that apply to non-EGCs, but any such election to opt out is irrevocable. We have irrevocably elected to opt out of this extended transition period provided by Section 102(b)(1) of the JOBS Act. Even though we have elected to opt out of the extended transition period, we may still take advantage of all of the other provisions of the JOBS Act, which include, but are not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, the reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and the exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

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, 2021, we had an accumulated deficit of approximately $197.4 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 planned drug product candidates and find strategic collaborators that can incorporate our planned products 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 planned drug product candidates in the United States or in any foreign market. Therefore, any estimated timing for our planned 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 planned 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 planned drug product candidates;
- regulatory approvals and marketing authorizations may not be achieved for our planned 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 planned 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 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 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 one of which is 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. 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 oncology programs in our CUE-100 series. We expect that additional trials of CUE-101 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 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 an IND or 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.

The continuing 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 continuing COVID-19 pandemic is evolving, and to date has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures. During 2020 and 2021, as a result of 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, to the extent those events and meetings are continuing. Many of these protocols remained in place during 2021.

As a result of the COVID-19 pandemic, or similar pandemics, 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 collaborator companies, 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, 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 anticipate filing by the end of the first quarter of 2022 based on the revised CUE-102 GMP manufacturing date provided by our CMO. 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.

These and other factors arising from the COVID-19 pandemic could worsen in the United States or locally at the location of our offices or clinical trials, each of which could further 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, 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 planned drug product candidates in preclinical studies may not be observed in human clinical trials. If clinical trials of our planned 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 planned 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 will acquire rights to develop, commercialize and sell specific Immuno-STATs relating to certain autoimmune disease and, in exchange for such rights, has agreed to make payments to us that include a licensing fee, milestone payments and sales royalties. The Merck Collaboration Agreement was amended in November 2020 to extend the research term and provide additional financial support through December 31, 2021 at which time the research term expired.

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. These agreements do not commit Merck or LG Chem to a long-term relationship, and they may disengage with us at any time.

In the first quarter of 2022, we determined to prioritize and strategically focus on our 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 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 planned 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 planned 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 planned 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 planned 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 planned drug product candidates could delay the development and commercialization of our planned drug product candidates in certain geographies for certain indications, which would harm our business prospects, financial condition, and results of operations.

Our collaboration agreements with Merck and LG Chem contain exclusivity provisions that restrict our research and development activities.

We have 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 are elected to be developed by Merck for two initial indications. So long as Merck continues product development on a Proposed Drug Product Candidate for an initial indication, we are 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.

Additionally, 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, the Company 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 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 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.

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 planned 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), cell therapies (e.g., Bristol-Myers Squibb, Gilead and Novartis), antibody-drug conjugates (e.g., Gilead, Roche, Seattle Genetics), immune checkpoint inhibitors (e.g., Bristol-Myers Squibb, Merck and Pfizer), and targeted cytokines (e.g., Bristol Myers Squibb/Nektar, Neoleukin, Roche 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, Kenneth Pienta, our Acting 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, 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 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 as a sole source of supply for manufacturing clinical supply of our lead product candidate, CUE-101. If we experience multiple successive batch failures, or if supply from Catalent is otherwise interrupted, there could be a significant disruption in our product candidate 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.

The manufacturing processes for CUE-101 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.

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 will 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 medicine 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 medicines 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. 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 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.” 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 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. Additionally, the fast-track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

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 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, there will have to be conducted 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 medicine, 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 medicine 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 medicine.

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 medicines, when and if any of them are approved.

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of medicines 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 medicines 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 medicines, manufacturers, or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such medicines, manufacturers, or manufacturing processes;
- restrictions on the labeling or marketing of a medicine;
- restrictions on the distribution or use of a medicine;
- requirements to conduct post-marketing clinical trials;
- receipt of warning or untitled letters;
- withdrawal of the medicines from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of medicines;
- 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 medicines;
- 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. Average review times at the agency have fluctuated in recent years as a result. 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 May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. 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 and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period. Regulatory authorities outside the U.S. 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 medicines 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, other healthcare providers 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, President Obama signed into law the PPACA. 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 have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect 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.

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 Trump 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, President Biden 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, President Trump 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 implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed by the Biden administration until January 1, 2023.

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). 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. 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 planned 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 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 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;
- 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 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. We also may be able to borrow, at our option, an additional $10.0 million, if we reach certain milestone events. 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 the 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.

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

We are an “emerging growth company,” or EGC, as defined in the JOBS Act. We will remain an EGC until the earlier of: (i) the last day of the fiscal year in which we have total annual gross revenue of $1.07 billion or more; (ii) December 31, 2022; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the last day of the first fiscal year in which the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- reduced disclosure obligations regarding executive compensation;
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved; and
- an exemption from compliance with the requirement of the Public Company Accounting Oversight Board regarding the communication of critical audit matters in the auditor’s report on the financial statements.

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not EGCs.

We are also 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. Similar to emerging growth companies, 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 may 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 that reports to the Securities and Exchange Commission and our management is required to devote substantial time to meet compliance obligations.

As a public company reporting to the Securities and Exchange Commission, or the SEC, 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 an "emerging growth company," 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.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our principal office is located in Cambridge, Massachusetts. We currently lease approximately 19,900 square feet of office and laboratory space. We use this space as our principal executive offices and for general office, research and development, and laboratory uses. In October 2021, the term of the lease was extended from June 2022 to March 2024 . The monthly rental rate is currently $375,000 until June 2022 and will increase to $388,000 for the remainder of the term. We also lease additional laboratory space consisting of three procedure and holding rooms. The monthly payments due under this lease agreement will be approximately $61,000 for the remainder of the lease term which expires in June 2022.

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 7, 2022, there were approximately 51 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.

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 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 our 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 continuing COVID-19 pandemic has prompted governments and regulatory bodies throughout the world to issue "stay-at-home" or similar orders, and enact restrictions on the performance of "non-essential" services, public gatherings and travel. Beginning in March 2020, we undertook precautionary measures 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, to the extent those events and meetings are continuing. We also established policies and procedures for all personnel who enter our company premises. The policies and procedures we implemented are consistent with the rules and guidelines recommended by the Centers for Disease Control and Prevention, the Commonwealth of Massachusetts and the City of Cambridge. However, these actions or additional measures we may undertake may ultimately delay progress of our developmental goals or otherwise negatively affect our business. In addition, third-party actions taken to contain the spread of the novel coronavirus, SARS-CoV-2, and mitigate public health effects may negatively affect our business. We do not believe any of these actions or disruptions have had a significant impact on our productivity or our operations. We continue to have many of these policies and procedures in place in 2021.

To date, we have experienced supply chain disruptions for lab supplies used in our preclinical research. In addition, January 2021, we were notified by our contract manufacturing organization, or 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 delay in the manufacturing of our CUE-102 GMP batch has impacted the expected filing date of the CUE-102 IND that was planned for the fourth quarter of 2021. The CUE-102 IND is now expected to be filed by the end of the first quarter of 2022 based on the revised CUE-102 GMP manufacturing date provided by our CMO.

Plan of Operation

Our technology is in the development phase. We believe that our licensed 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 those described below under the headings "Collaboration Agreement with Merck" and "Collaboration Agreement with LG Chem".

Critical Accounting Policies and Significant Judgments and Estimates

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 as of December 31, 2021.

Revenue Recognition

We follow the provisions of Accounting Standards Codification, or ASC, 606, *Revenue from Contracts with Customers*. We generate revenue solely through collaboration arrangements with strategic partners for the development and commercialization of drug product candidates. The core principle of ASC 606 is that an entity should recognize revenue to depict the transfer of promised goods and/or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods and/or services. To determine the appropriate amount of revenue to be recognized for arrangements that we determine are within the scope of ASC 606, we perform the following steps: (i) identify the contract(s) with the customer, (ii) identify the performance obligations in the contract, (iii) determine the transaction price, (iv) allocate the transaction price to the performance obligations in the contract and (v) recognize revenue when (or as) each performance obligation is satisfied.

We recognize collaboration revenue under certain of our license or collaboration agreements that are within the scope of 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 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. 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 two open contracts. 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. Currently, we have one contract with an option to acquire additional goods and/or services in the form of additional research and development services for additional drug product candidates.

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 expense recognition is more appropriate. Other research and development expenses are charged to operations as incurred. Payments made pursuant to research and development contracts are initially recorded as research and development contract advances in our balance sheet and then charged to research and development expenses in our consolidated statements of operations and comprehensive loss as those contract services are performed. Expenses incurred under research and development contracts in excess of amounts advanced are recorded as research and development contract liabilities in our balance sheet, with a corresponding charge to research and development expenses in our consolidated statements of operations and comprehensive loss.

Nonrefundable advance payments for future research and development activities pursuant to an executory contractual arrangement are recorded as advances as described above. 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. 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 adjusts 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, non-employees and consultants for services rendered. Such issuances vest and expire according to terms established at the issuance date.

Stock-based payments to officers, directors, members of our Scientific and Clinical Advisory Board, non-employees and outside consultants and employees, 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 lack of history and option activity, we utilize the simplified method to estimate the expected term of options at the date of grant. The fair value of common stock is determined by reference to either recent or anticipated cash transactions involving the sale of our common stock.

We recognize the fair value of stock-based compensation in general and administrative expenses and in research and development expenses in our consolidated statements of operations and comprehensive loss, depending on the type of services provided by the recipient of the equity award. We issue new shares of common stock to satisfy stock option exercises.

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

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, 2021, 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, 2021 and 2020.

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 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, 2021 and 2020, costs incurred with respect to the Einstein License aggregated $619,000 and $75,000, respectively. Such costs are included in research and development costs in the consolidated statements of operations and 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 view the Merck Collaboration Agreement as a component of our development strategy since it will allow 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 entails (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.

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 are elected to be developed by Merck. So long as Merck continues product development on a Proposed Product Candidate, we are 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. Additionally, we may be eligible to receive 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. Excluding the $2.5 million up-front payment described above, we are eligible to earn up to $101.0 million for the achievement of certain research and development milestones, $120.0 million for the achievement of certain regulatory milestones and $150.0 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 are achieved. The Merck Collaboration Agreement requires us to use the first $2.5 million of milestone payments we receive under the agreement to fund contract research. The amount of the royalty payments is a percentage of product sales ranging in the single digits based on the amount of such sales. We recorded approximately $2,155,000 in revenue for the year ended December 31, 2021 related to the Merck Collaboration Agreement, compared to $177,000 for the year ended December 31, 2020.

The term of the Merck Collaboration Agreement extends until the expiration of all royalty obligations following a product candidate’s receipt of marketing authorization, at which point Merck’s licenses and sublicenses granted under the agreement shall become fully paid-up, perpetual licenses and sublicenses, as applicable. Royalties on each product subject to the Merck Collaboration Agreement shall continue on a country-by-country basis until the expiration of the later of: (1) the last-to-expire patent claiming the compound on which such product is based and (2) a period of ten years after the first commercial sale of such product in such country.

Notwithstanding the foregoing, Merck may terminate the Merck Collaboration Agreement at any time upon 30 days’ notice to us. The Merck Collaboration Agreement may also be terminated by either party if the other party is in breach of its obligations thereunder and fails to cure such breach within 90 days after notice or by either party if the other party files for bankruptcy or other similar insolvency proceedings.

On November 18, 2020, we entered into a First Amendment to the Merck Collaboration Agreement, or the Amendment, with Merck. Pursuant to rights granted to Merck under the Merck Collaboration Agreement, the Amendment extended the term of the research program under the Merck Collaboration Agreement for an additional year until December 31, 2021. Under the terms of the 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 for this milestone payment pursuant to our revenue recognition policy in relation to the performance of our obligations to develop Immuno-STAT drug product candidates under the arrangement. The term of the research program under the Merck Collaboration Agreement expired on December 31, 2021.

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, 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 Wilm's Tumor 1, or WT1, as the first target antigen for a Product Candidate under the LG Chem Collaboration Agreement. In June 2021, after ongoing discussions regarding the selection of the second of the two additional cancer antigens, we agreed with LG Chem to let the selection period 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. 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 $5.8 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 U.S. Food and Drug Administration's, or 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 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. The amount of fees and milestone payments, as well as whether we receive royalty payments, will depend on the number of alleles selected by LG Chem and whether we exercise our option to co-develop and co-commercialize the additional program worldwide, in which case we would share costs and profits instead of receiving royalties and post-option-exercise milestones. For the years ended December 31, 2021 and 2020, we recognized approximately $12,786,000 and $2,978,000, respectively, in collaboration revenue related to this agreement.

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, including higher legal, accounting, insurance, compliance, compensation and other expenses.

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 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 increase our efforts to advance the clinical development of CUE-101 and CUE-102, including our ongoing and planned clinical trials, and develop technology for potential future products based on our technology and research.

Years Ended December 31, 2021 and 2020

Our consolidated statements of operations and comprehensive loss for the years ended December 31, 2021 and 2020, as discussed herein are presented below.

	Years Ended December 31,	
	2021	2020
Collaboration revenue	$ 14,941,370	$ 3,154,325
Operating expenses:		
General and administrative	17,306,678	14,651,205
Research and development	41,346,765	33,545,705
Total operating expenses	58,653,443	48,196,910
Loss from operations	(43,712,073)	(45,042,585)
Other income:		
Interest income, net	45,898	463,914
Total other income	45,898	463,914
Loss before provision for income taxes	(43,666,175)	(44,578,671)
Provision for income taxes	(495,000)	(206,250)
Net loss	$ (44,161,175)	$ (44,784,921)
Unrealized (loss) gain from available-for-sale securities	(7,131)	17,452
Comprehensive loss	$ (44,168,306)	$ (44,767,469)
Net loss per common share – basic and diluted	$ (1.41)	$ (1.56)
Weighted average common shares outstanding – basic and diluted	31,285,418	28,688,625

Collaboration Revenue

Collaboration revenue totaled approximately $14,941,000 and $3,154,000 for the years ended December 31, 2021 and 2020, respectively. This increase of approximately $11,787,000 was due primarily to cost sharing earned from the performance of collaboration services under the LG Chem Collaboration Agreement during 2021, the $3,000,000 milestone achieved in November 2021 for the selection of a clinical product candidate under the LG Chem Collaboration Agreement, and revenue related to the Merck Collaboration Agreement. 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 $17,307,000 and $14,651,000 for the years ended December 31, 2021 and 2020, respectively. This increase of approximately $2,656,000 was due primarily to higher stock-based compensation related to executive management, professional and consulting fees, employee and board compensation and other business expenses related to the ongoing management of the company. We expect our general and administrative expenses to increase as we are required to comply with certain regulatory and legal requirements.

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.

General and administrative expenses for the year ended December 31, 2020 included expenses related to professional and consulting fees of approximately $4,483,000, stock-based compensation of $4,094,000, employee and board compensation of $3,875,000, rent of $1,082,000, and other general and administrative expenses totaling $1,117,000.

Research and Development

Research and development expenses totaled approximately $41,347,000 and $33,546,000 for the years ended December 31, 2021 and 2020, respectively. This increase of approximately $7,801,000 was due primarily to higher laboratory and drug substance manufacturing costs, employee and Scientific and Clinical advisory board compensation, other professional fees, licensing fees and rent.

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, other professional fees of $1,400,000, depreciation and amortization of $1,154,000, and other research and development related expenses totaling $2,448,000.

Research and development expenses for the year ended December 31, 2020 included expenses related to research and laboratory expenses of approximately $8,420,000, employee and Scientific and Clinical Advisory Board compensation of $7,886,000, stock-based compensation of $6,387,000, clinical expenses of $4,264,000, rent of $3,511,000, depreciation and amortization of $960,000, and other research and development related expenses of $2,118,000.

Interest Income

Interest income was approximately $46,000 for the year ended December 31, 2021, as compared to approximately $464,000 for the year ended December 31, 2020. The majority of our marketable securities matured in early 2021 and we made no additional investment in marketable securities in 2021. The interest income earned from marketable securities in 2021 was immaterial. Interest income for the year ended December 31, 2021 included approximately $4,600 in expense resulting from amortization of discounts received on certain of our marketable securities, compared to approximately $80,000 of other income for the year ended December 31, 2020.

Foreign Withholding Taxes

Provision for income tax for the years ended December 31, 2021 and 2020 was comprised of $495,000 and approximately $206,000, respectively, in foreign income tax expense on LG Chem milestone payments in each year.

Net Loss

As a result of the foregoing, our net loss was approximately $44,161,000 for the year ended December 31, 2021, as compared to approximately $44,785,000 for the year ended December 31, 2020.

Liquidity and Capital Resources

We have financed our working capital requirements primarily through private and public offerings of equity securities, "at-the-market", or ATM, equity sales, cash received from Merck and LG Chem under their respective collaboration agreements and borrowing under the Loan and Security Agreement, or the Loan Agreement, with Silicon Valley Bank, or SVB. At December 31, 2021 and December 31, 2020, we had unrestricted cash, cash equivalents and marketable securities totaling approximately $64,400,000 and approximately $84,900,000, 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 report.

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.

In March 2020, we entered into an ATM, equity offering sales agreement, or the March 2020 Sales Agreement, with Stifel Nicolaus & Company, Inc., or Stifel, to sell shares of our common stock for aggregate gross proceeds of up to $35.0 million, from time to time, through an “at-the-market” equity offering program under which Stifel acts as sales agent. As of December 31, 2020, we had sold a total of 1,824,901 shares of common stock under the March 2020 Sales Agreement for proceeds of approximately $34.3 million, net of commissions paid, but excluding estimated transaction expenses. Due to the issuance and sale of all the shares of common stock subject thereto, the March 2020 Sales Agreement terminated in accordance with its terms.

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 Sales Agreement, with 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 acts as sales agent. During the year ended December 31, 2021, we 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. As of December 31, 2021, we sold 2,099,700 shares of common stock under the June 2020 Sales Agreement for proceeds of $32.7 million, net of commissions paid, but excluding estimated transaction expenses. The June 2020 Sales Agreement terminated in October 2021 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 LLC. During the year ended December 31, 2021, we sold 476,187 shares of common stock under the October 2021 ATM Agreement for proceeds of $7 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. We also may be able to borrow, at our option, an additional $10.0 million, if we reach certain milestone events. 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 repayment in full of the Term Loans, the Company will be required to pay a final payment fee equal to 5.00% of the original principal amount of any funded term loan being repaid.

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, 2021 and 2020:

	December 31, 2021	December 31, 2020
Net cash provided by (used in):		
Operating activities	$ (38,837,166)	$ (32,494,034)
Investing activities	9,108,511	4,455,874
Financing activities	19,233,322	58,614,263
Net (decrease) increase in cash, cash equivalents, and restricted cash	$ (10,495,333)	$ 30,576,103

Operating Activities

During the year ended December 31, 2021, we used cash of approximately $38,837,000 in operating activities, as compared to approximately $32,494,000 of cash used in operating activities during the year ended December 31, 2020. Cash used during the year ended December 31, 2021 consisted primarily of our net loss of approximately $44,161,000, and increases 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.

Cash used during the year ended December 31, 2020 consisted primarily of our net loss of approximately $44,785,000, and increases of approximately $4,203,000 in operating lease right-of-use asset, $662,000 in accounts receivable, $563,000 in other non-cash charges, $381,000 in prepaid expenses, and $5,000 in other assets. Cash used was partially offset by increases of approximately $4,679,000 in operating lease liability, $741,000 in accounts payable, and $560,000 in accrued expenses, $503,000 in research and development contract liabilities, as well as non-cash charges of approximately $1,057,000 in depreciation and amortization, $10,481,000 in stock-based compensation expense, and $84,000 in amortization of premium/discount on purchased securities.

Investing Activities

During the year ended December 31, 2021, we generated cash of approximately $9,109,000 from investing activities, compared to approximately $4,456,000 generated by investing activities during the year ended December 31, 2020. Cash generated during the year ended December 31, 2021 consisted primarily of approximately $10,000,000 for the redemption of short-term investments, cash received for sale of fixed assets of approximately $22,000, offset by the purchase of property and equipment of approximately $913,000. Cash generated during the year ended December 31, 2020 consisted primarily of approximately $15,000,000 for the redemption of short-term investments offset by the purchase of property and equipment of approximately $595,000 and the purchase of marketable securities of $9,949,000.

Financing Activities

During the year ended December 31, 2021, we generated cash from financing activities of approximately $19,233,000, compared to approximately $58,614,000 during the year ended December 31, 2020. 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. Cash generated during the year ended December 31, 2020 consisted primarily of cash proceeds from the common stock sold through our ATM sales agreements with Stifel of approximately $56,682,000, net of underwriting commissions and fees, and the exercise of common stock options of approximately $2,203,000, and restricted stock awards net of taxes withheld of $271,000.

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, CUE-102, CUE-103 and Neo-STAT;
- leverage our programs to advance our other drug product candidates into preclinical and clinical development;
- seek regulatory approvals for any drug product candidates that successfully complete clinical trials;
- seek to 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, 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 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 our programs outside of oncology, including our CUE-200, CUE-300 and CUE-400 series.

We believe that our existing cash resources as of December 31, 2021 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 research, development and commercialization of 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 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;
- 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 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 January 18, 2018, we entered into an operating lease agreement for our laboratory and office space in Cambridge, Massachusetts for the period from May 1, 2018 through April 30, 2021, or the Laboratory and Office Lease. The lease contains escalating payments during the lease period. Upon execution 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. We also prepaid seven and one half months' rent pursuant to an amendment to the lease agreement executed on June 18, 2018. We record monthly rent expense on a straight-line basis, equal to the total of the lease payments over the lease term divided by the number of months of the lease term.

On June 18, 2018, we entered into an amendment to the Laboratory and Office Lease that provide us with a reduction in rental fees for our office and laboratory space in exchange for prepayment of a portion of the fees. This amendment was effective beginning on May 15, 2018 and expires on April 14, 2021. The monthly rent payment due under the Laboratory and Office Lease is currently approximately $331,000 until April 2021 and will increase to approximately $375,000 for the remainder of the term.

On September 20, 2018, we entered into an operating lease for additional laboratory space at 21 Erie Street, Cambridge, Massachusetts for the period from October 15, 2018 through April 14, 2021, or the Additional Laboratory Lease. The lease contains escalating payments during the lease period. The monthly rental rate under the Additional Laboratory Lease was approximately $73,000 for the first 12 months and approximately $79,000 for the remainder of the term. Upon execution of this lease agreement, we prepaid 12 months' rent pursuant to the lease agreement executed on September 20, 2018.

On September 19, 2019, we entered into a second amendment to the Additional Laboratory Lease that removed one holding room from the additional laboratory space. The amendment was effective beginning on October 1, 2019 and expires on April 14, 2021. The monthly rental rate under the Additional Laboratory Lease decreased from approximately $79,000 to approximately $59,000 for the remainder of the lease term.

On June 24, 2020, we entered into a second amendment to the Laboratory and Office Lease. Pursuant to the amendment (1) the term of the lease was extended to June 14, 2022 and (2) the monthly rental rate for the last 14 months of the lease term was increased to approximately $375,000. We determined that the amendment should be accounted for as a lease modification under Accounting Standards Codification 842, *Leases*, or ASC 842, not as a separate contract, with an effective date of lease modification of May 14, 2020. At the effective date of modification, we recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $4,826,000.

On July 20, 2020, we entered into a third amendment to the Additional Laboratory Lease. Pursuant to the amendment the term of the lease was extended to June 14, 2022. We determined that the amendment should be accounted for as a lease modification under ASC 842, not as a separate contract, with an effective date of lease modification of August 4, 2020, when the agreement was fully executed. At the effective date of modification, we recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $813,000.

On October 22, 2021, the Company entered into a third amendment to the Laboratory and Office Lease. Pursuant to the amendment (1) the term of the lease was extended to March 14, 2024 and (2) the monthly rental rate for the last 21 months of the lease term was increased from approximately $375,000 to approximately $388,000. We determined that the amendment should be accounted for as a lease modification under ASC 842, not as a separate contract, with an effective date of lease modification of November 1, 2021, when the agreement was fully executed. At the effective date of modification, we recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $7,616,000.

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, 2021, we owed Catalent approximately $1,255,000 which was fully accrued for on December 31, 2021.

Einstein License Agreement

The Company's 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 we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the SEC's 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, 2021, 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, 2021, 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, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

This annual report does not include an attestation report of our registered public accounting firm due to the transition period established by the JOBS Act for emerging growth companies.

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 2022 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 is incorporated by reference to our Proxy Statement on Schedule 14A relating to our 2022 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 2022 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 2022 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 2022 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, 2021 and 2020, 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, 2021 and 2020, 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.

/s/ RSM US LLP

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

Boston, Massachusetts
March 16, 2022

CUE BIOPHARMA, INC.

CONSOLIDATED BALANCE SHEETS

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash and cash equivalents	$ 64,370,800	$ 74,866,133
Marketable securities	—	10,002,550
Accounts receivable	3,142,527	1,417,482
Prepaid expenses and other current assets	954,792	1,241,239
Total current assets	68,468,119	87,527,404
Property and equipment, net	2,111,949	2,108,024
Operating lease right-of-use assets	9,809,876	6,774,229
Deposits	2,720,991	2,572,476
Restricted cash	150,000	150,000
Other long term assets	140,000	401,667
Total assets	$ 83,400,935	$ 99,533,800
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,590,701	$ 2,070,303
Accrued expenses	4,619,963	2,787,211
Research and development contract liability, current portion	645,345	6,681,025
Operating lease liabilities, current portion	4,931,675	4,777,427
Total current liabilities	12,787,684	16,315,966
Research and development contract liability, net of current portion	—	1,937,575
Operating lease liabilities, net of current portion	5,121,179	2,368,787
Total liabilities	17,908,863	20,622,328
Commitments and contingencies (NOTE 14)		
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 – 32,202,496 shares and 30,351,366 shares at December 31, 2021 and 2020, respectively	32,202	30,351
Additional paid-in capital	262,906,084	232,159,029
Accumulated other comprehensive income	—	7,131
Accumulated deficit	(197,446,214)	(153,285,039)
Total stockholders' equity	65,492,072	78,911,472
Total liabilities and stockholders' equity	$ 83,400,935	$ 99,533,800

See accompanying notes to consolidated financial statements.

CUE BIOPHARMA, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

	Years Ended December 31,	
	2021	**2020**
Collaboration revenue	$ 14,941,370	$ 3,154,325
Operating expenses:		
General and administrative	17,306,678	14,651,205
Research and development	41,346,765	33,545,705
Total operating expenses	58,653,443	48,196,910
Loss from operations	(43,712,073)	(45,042,585)
Other income:		
Interest income, net	45,898	463,914
Total other income	45,898	463,914
Loss before provision for income taxes	$ (43,666,175)	$ (44,578,671)
Provision for income taxes	(495,000)	(206,250)
Net loss	(44,161,175)	(44,784,921)
Unrealized (loss) gain from available-for-sale securities	(7,131)	17,452
Comprehensive loss	$ (44,168,306)	$ (44,767,469)
Net loss per common share – basic and diluted	$ (1.41)	$ (1.56)
Weighted average common shares outstanding – basic and diluted	31,285,418	28,688,625

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, 2019	26,562,178	$ 26,562	$ 163,067,773	$ (10,321)	$ (108,500,118)	$ 54,583,896
Issuance of common stock from public offerings, net of underwriter commissions and fees	3,016,901	3,017	56,679,219	—	—	56,682,236
Stock-based compensation	—	—	10,480,782	—	—	10,480,782
Exercise of stock options	454,497	454	2,202,607	—	—	2,203,061
Issuance of common stock upon cashless exercise of warrants, net of shares withheld	278,179	278	(278)	—	—	—
Restricted stock awards	56,665	57	(40)	—	—	17
Repurchase of restricted stock awards	(17,054)	(17)	(271,034)	—	—	(271,051)
Unrealized gains from available-for-sale securities	—	—	—	17,452	—	17,452
Net loss	—	—	—	—	(44,784,921)	(44,784,921)
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)	—	—	(0)
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

See accompanying notes to consolidated financial statements.

CUE BIOPHARMA, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Years Ended December 31, 2021	Years Ended December 31, 2020
Cash flows from operating activities:		
Net loss	$ (44,161,175)	$ (44,784,921)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	1,257,662	1,057,458
Stock-based compensation	11,515,584	10,480,782
Change in operating lease right-of-use asset amortization	(3,035,647)	(4,202,480)
Amortization of premium/discount on purchased securities	(4,581)	83,694
Gain on disposal of fixed asset	(21,550)	—
Other non-cash charges	—	(563,232)
Changes in operating assets and liabilities:		
Account receivable	(1,725,045)	(662,584)
Prepaid expenses and other current assets	(50,434)	(381,132)
Other assets	250,000	(4,971)
Deposits	(148,515)	—
Accounts payable	520,398	741,265
Accrued expenses	1,832,752	559,859
Research and development contract liability	(7,973,255)	503,263
Operating lease liability	2,906,640	4,678,965
Net cash used in operating activities	(38,837,166)	(32,494,034)
Cash flows from investing activities:		
Purchases of property and equipment	(913,039)	(595,259)
Cash received from sale of fixed asset	21,550	—
Redemption of short term investments	10,000,000	15,000,000
Purchases of marketable securities	—	(9,948,867)
Net cash provided by investing activities	9,108,511	4,455,874
Cash flows from financing activities:		
Proceeds from the public offering of common stock, net of underwriter's commission and fees	17,384,668	56,682,236
Issuance of restricted stock awards	55	17
Proceeds from the exercise of stock options	2,598,782	2,203,061
Restricted stock awards withheld at vesting to cover taxes	(750,183)	(271,051)
Net cash provided by financing activities	19,233,322	58,614,263
Net (decrease) increase in cash, cash equivalents, and restricted cash	(10,495,333)	30,576,103
Cash, cash equivalents, and restricted cash at beginning of year	75,016,133	44,440,030
Cash, cash equivalents, and restricted cash at end of year	$ 64,520,800	$ 75,016,133
Supplemental disclosures of cash flow information:		
Cash paid for –		
Purchases of property and equipment in accounts payable or accrued expenses	$ —	$ 446,372
Operating lease modification	$ 7,616,000	$ 5,639,000

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 Cambridge, Massachusetts.

The Company is a clinical-stage biopharmaceutical company engineering a novel class of injectable biologics to selectively engage and modulate targeted T cells within the patient's body to treat a broad range of cancers, chronic infectious diseases, and autoimmune disorders.

The Company is in the development stage and has incurred recurring losses and negative cash flows from operations. As of December 31, 2021, the Company had unrestricted cash, cash equivalents and marketable securities of approximately $64.4 million. Management believes that current cash, cash equivalents and marketable securities on hand at December 31, 2021 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 increased 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, 2021 and 2020, 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 Corporation, Inc., 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 March 2020, the Company entered into an "at-the-market" ("ATM") equity offering sales agreement with Stifel Nicolaus & Company, Inc. ("Stifel") (the "March 2020 ATM Agreement") to sell shares of the Company's common stock for aggregate gross proceeds of up to $35 million, from time to time, through an ATM equity offering program under which Stifel would act as sales agent. As of December 31, 2020, the Company had sold a total of 1,824,901 shares of common stock under the March 2020 ATM Agreement for proceeds of approximately $34.3 million, net of commissions paid, but excluding estimated transaction expenses. Due to the issuance and sale of all the shares of common stock subject thereto, the March 2020 ATM Agreement terminated in accordance with its terms.

In June 2020, the Company entered into an ATM equity offering sales agreement with Stifel (the "June 2020 ATM Agreement") 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. During the year ended December 31, 2021, the Company sold 907,700 shares of common stock under the June 2020 ATM Agreement for proceeds of approximately $10.4 million, net of commissions paid, but excluding transaction expenses. As of December 31, 2021, 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. As of December 31, 2021, the Company sold an aggregate 476,187 shares of common stock under the October 2021 ATM Agreement for proceeds of approximately $7.0 million, net of commissions paid, but excluding transaction expenses.

Consolidation

The accompanying consolidated financial statements include the Company and its wholly owned subsidiary, Cue Biopharma Securities Corporation, Inc. The Company has eliminated all intercompany transactions for the years presented.

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 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.

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.

Cash and Cash Equivalents

The Company considers all 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 are recognized and are included in other comprehensive income (loss). Realized gains are recognized and determined on a specific identification basis and are included in other income (loss) on the income statement. Amortization and accretion of discounts and premiums is recorded in interest income. The Company currently invests in United States 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, 2021 and 2020.

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 disposition 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 in and 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.

As the Company can renew the underlying rights to the CUE BIOLOGICS Mark indefinitely at nominal cost, this acquired intangible asset has been classified as a component of other long term assets, having a useful life of 15 years. The Company recorded $11,666 in amortization related to the trademark at December 31, 2021 and 2020.

Revenue Recognition

The Company follows the provisions of Accounting Standards Codification 606, *Revenue from Contracts with Customers* ("ASC 606"). The Company generates revenue solely through collaboration arrangements with strategic partners for the development and commercialization of drug product candidates. The core principle of ASC 606 is that an entity should recognize revenue to depict the transfer of promised goods and/or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods and/or services. To determine the appropriate amount of revenue to be recognized for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following steps: (i) Identify the contract(s) with the customer, (ii) Identify the performance obligations in the contract, (iii) Determine the transaction price, (iv) Allocate the transaction price to the performance obligations in the contract and (v) Recognize revenue when (or as) each performance obligation is satisfied.

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. 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. Currently, the Company has one contract with an option to acquire additional goods and/or services in the form of additional research and development services for additional drug product candidates which it evaluated and determined that it was not a material right related to the LG Chem Agreement.

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 operations as incurred. For the years ended December 31, 2021 and 2020, patent expenses were approximately $2,259,000 and $1,879,000, respectively. Patent expenses are included in general and administrative expenses in the Company's consolidated statements of operations and comprehensive loss.

Licensing Fees and Costs

Licensing fees and costs consist primarily of costs relating to the acquisition of the Company's license agreement with the Albert Einstein College of Medicine, including related royalties, maintenance fees, milestone payments and product development costs. Licensing fees and costs are charged to operations 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, 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. There were no sales of lab equipment or capital equipment during the year ended December 31, 2020.

Leases

The Company recognizes each of its long-term operating leases as a right-of-use asset and a lease liability on its consolidated balance sheet. The lease liability is determined as the present value of future lease payments using an estimated rate of interest that the Company would have to pay to borrow equivalent funds on a collateralized basis at the lease commencement date. The right-of-use asset is based on the liability adjusted for any defer rent. The Company determines if an arrangement is, or contains, a lease at contract inception and during modifications or renewal of existing leases. The lease term at the commencement date is determined by considering whether renewal options and termination options are reasonably assured of exercise.

Right-of-use assets and lease liabilities are remeasured upon certain modifications to leases using the present value of remaining lease payments and estimated incremental borrowing rate upon lease modification. Operating lease cost is recognized on a straight-line basis over the lease term. The Company recognized variable lease payments as operating expenses in the period in which the obligation for those payments is incurred. Variable lease payments primarily include common area maintenance, utilities, real estate taxes, insurance, and other operating costs that are passed on from the lessor in proportion to the space the Company leases.

Stock-Based Compensation

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

Stock-based payments to officers, directors, members of the Company's Scientific and Clinical Advisory Board, non-employees and outside consultants and employees, 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 exercise price is determined based on the fair value of the Company's common stock at the date of grant. The Company accounts for forfeitures as they occur.

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 statements of operations, 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.

The Company recognized approximately $495,000 and $206,250 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 years ended December 31, 2021 and 2020, respectively.

The Company recognizes interest accrued relative to unrecognized tax benefits in interest expense and penalties in operating expense. During the years ended December 31, 2021 and 2020, 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, 2021 and 2020.

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 loss includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. The Company's only element of other comprehensive loss in all periods presented, other than its net loss, was unrealized gains and losses 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, 2021 and 2020, the Company excluded the outstanding securities summarized below, which entitle 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,	
	2021	**2020**
Common stock warrants	851,969	861,969
Common stock options	5,654,168	5,030,899
Nonvested restricted stock units	98,335	230,002
Total	6,604,472	6,122,870

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 $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 Company had $72,943,275 in cash equivalents and $10,002,550 in short-term marketable securities that were measured and recorded at fair value on the Company's balance sheet at December 31, 2020.

The carrying value of financial instruments (consisting of cash, a certificate of deposit, 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 ("FASB") issued Accounting Standards Update ("ASU") No. 2016-13, *Financial Instruments- Credit Losses: Measurement of Credit Losses on Financial Instruments (ASC 326) (CECL)*. The 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 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 is still evaluating the impact of ASU 2016-13 on the Company's consolidated financial statements, if any.

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*, which is intended to simplify various aspects related to accounting for income taxes. The pronouncement became effective for fiscal years, and for interim periods within those fiscal years, beginning after December 15, 2020. ASU No. 2019-12 is effective for the Company beginning in the fiscal year ended December 31, 2021. The Company adopted ASU No. 2019-12 on January 1, 2021 and it did not have a material impact on the Company's financial position, results of operations or disclosures.

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 generally accepted accounting principles 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, 2021 and 2020 and indicate the level of the fair value hierarchy utilized to determine such fair value:

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

	Fair Value Measurements as of December 31, 2020			
	Level 1	**Level 2**	**Level 3**	**Fair Value**
Cash equivalents	$ 72,943,275	$ —	$ —	$ 72,943,275
Marketable securities	—	10,002,550	—	10,002,550
Total	$ 72,943,275	$ 10,002,550	$ —	$ 82,945,825

As of December 31, 2021 and 2020, the Company's cash equivalents that are invested in money market funds valued using Level 1 inputs for identical securities. The Company measures the fair value of marketable securities that are invested in United States Treasury securities using Level 2 inputs and primarily relies on quoted prices in active markets for similar marketable securities. During the years ended December 31, 2021 and 2020, there were no transfers between Level 2 and Level 3.

4. Marketable Securities

As of December 31, 2021, the Company did not have any marketable securities. As of December 31, 2020, the fair value of available-for-sale marketable securities by type of security was as follows:

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. Treasury Securities	$ 9,995,419	$ 7,131	$ —	$ 10,002,550
	$ 9,995,419	$ 7,131	$ —	$ 10,002,550

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. At December 31, 2020, the Company marketable securities consisted of $10,002,550 of investments that mature within twelve months. The Company recognized an unrealized gain on investments of $17,452 for the year ended December 31, 2020.

5. Property and Equipment

Property and equipment as of December 31, 2021 and 2020 is summarized as follows:

	December 31,	
	2021	2020
Laboratory equipment	$ 5,203,166	$ 4,148,426
Furniture and fixtures	93,322	93,321
Computer equipment	252,804	267,837
Leasehold-Improvements	6,530	—
Construction in progress	—	405,019
	5,555,822	4,914,603
Less accumulated depreciation	(3,443,873)	(2,806,579)
Net property and equipment	$ 2,111,949	$ 2,108,024

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. Depreciation expense for the year ended December 31, 2020 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 $265,262.

	Years Ended December 31,	
	2021	2020
General and administrative	$ 14,401	$ 20,301
Research and development	894,713	760,228
Total	$ 909,114	$ 780,529

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. The Company did not sell lab equipment or other capital equipment during the year ended December 31, 2020.

6. Accrued Expenses

Accrued expenses as of December 31, 2021 and 2020 is summarized as follows:

	December 31,	
	2021	2020
Employee and board compensation	$ 2,006,465	$ 1,963,983
Contract manufacturing services	1,273,978	108,880
Professional Services	352,114	326,028
Contract research services	987,406	388,320
	$ 4,619,963	$ 2,787,211

7. 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, 2021, $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, 2021 and 2020.

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 10 Collaboration Agreement with LG Chem.

8. 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, 2021, the Company granted stock options to purchase 1,251,000 shares of the Company's common stock and 0 restricted stock units, 382,219 shares of common stock were exercised, 245,512 shares of common stock were cancelled, and 131,667 restricted stock units were released. At December 31, 2021, stock options for 4,937,903 shares of common stock and 320,000 restricted stock units had been granted and 571,990 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, 2021, stock options for a total of 5,432,503 shares of common stock and 320,000 restricted stock units had been granted and 577,390 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, 2021 and 2020, the fair value of each stock option award was estimated using the Black-Scholes option-pricing model utilizing the following assumptions:

	December 31,	
	2021	**2020**
Risk-free interest rate	0.61 to 1.43%	0.38 to 1.56%
Expected dividend yield	0%	0%
Expected volatility	92.8-100.9%	93.4-99.6%
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, 2021 is as follows:

	Number of Shares		Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in Years)
Stock options outstanding at December 31, 2019	4,793,253	$	7.10	5.64
Granted	981,800		17.31	
Exercised	(454,497)		4.86	
Cancelled	(289,657)		10.14	
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
Stock options exercisable at December 31, 2021	3,558,987	$	8.31	3.81

The Company recognized, $9,588,811 and $8,861,760, in stock-based compensation during the years ended December 31, 2021 and 2020, respectively, related to stock option activity. As of December 31, 2021, total unrecognized stock-based compensation was approximately $17,521,334, which is expected to be recognized as an operating expense in the Company’s consolidated statements of operations and comprehensive loss through March 2024.

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. The aggregate intrinsic value of options is calculated as the difference of the market close price of $11.31 on December 31, 2021, and the weighted average exercise price of $8.31, with a weighted average remaining contractual term of less than one year.

The aggregate intrinsic value of exercisable but unexercised in-the-money stock options at December 31, 2020 was approximately $16,869,399 based on a weighted average exercise price of $7.05 per share at December 31, 2020.

Option Amendments - Modification of Incentive Stock Options

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.

During the year ended December 31, 2020, the following event resulted in the amendment to terms of outstanding stock option awards:

On January 22, 2020, 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 January 21, 2020, the terminated employee held outstanding options to purchase an aggregate of 215,000 shares of the Company's common stock at a weighted average exercise price of $6.22 per share, including unvested options to purchase 94,375 shares at a weighted average exercise price of $7.83 per share. On January 21, 2020, 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 12 months from the date of the termination. In May 2020, the final separation agreement was amended to extend the post-employment option exercise period from 12 months to 36 months.

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 $344,850, which was expensed in the year ended December 31, 2020.

Restricted Stock Units

On October 3, 2019, the Company granted 100,000 restricted stock units ("RSUs") with time-based vesting conditions to certain executives. During the year ended December 31, 2019, the Company awarded 100,000 RSUs at an average grant date fair value of $7.53 per share. The RSUs vest in three substantially equal installments beginning on grant date, and annually 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 vest on September 30, 2021, and the balance vest on March 31, 2022, subject to the recipient's continued service on each applicable vesting date. On March 31, 2020, the Company granted 50,000 RSUs with time-based vesting conditions to an executive officer. The RSUs vest in three substantially equal installments beginning on the grant date, and annually thereafter, subject to the recipient's continued service on each applicable vesting date. 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 substantially equal installments beginning on the grant date, and annually 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 for the under the Omnibus Plan for the year ending December 31, 2021:

Restricted Securities	**Number of Shares**	**Weighted Average Grant Date Fair Value Per Share**
Nonvested balance at December 31, 2020	230,002	$ 16.66
Vested/Released	(131,667)	$ 15.51
Nonvested balance at December 31, 2021	98,335	$ 18.21

The Company recognized $1,926,773 and $1,619,022 in stock-based compensation during the years ended December 31, 2021 and 2020, respectively, related to restricted stock unit activity. As of December 31, 2021, total unrecognized stock-based compensation was approximately $846,072, which is expected to be recognized as an operating expense in the Company's consolidated statements of operations and comprehensive loss less than one year.

Stock-based Compensation

Stock-based compensation for the years ended December 31, 2021 and 2020 was included in the consolidated statements of operations and comprehensive loss as follows:

	December 31,	
	2021	**2020**
General and administrative	$ 5,307,982	$ 4,093,542
Research and development	6,207,602	6,387,240
Total	$ 11,515,584	$ 10,480,782

9. Warrants

The Company has two tranches of common stock warrants outstanding at December 31, 2021. The first tranche was exercisable for 370,370 shares of common stock issued on June 15, 2015 with an exercise price of $2.70 per share. These warrants were issued with a seven year term and expire on June 15, 2022. The second tranche was exercisable for 882,071 shares of common stock issued on December 27, 2017 with an exercise price of $9.38 per share. These warrants were issued with a five year term and expire on December 26, 2022. The intrinsic value of exercisable but unexercised in-the-money common stock warrants at December 31, 2021 was approximately $2,062,542 based on a fair value of $11.31 per share on December 31, 2021.

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 following table summarizes common stock warrant activity for the year ended December 31, 2021:

	Warrant Issued June 15, 2015 Tranche 1	Warrant Issued December 27, 2017 Tranche 2	Total
Balance at December 31, 2020	72,611	789,358	861,969
Issued via cashless exercises	(8,048)		(8,048)
Withheld as payment to cover issued shares	(1,952)		(1,952)
Balance at December 31, 2021	62,611	789,358	851,969

10. 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 views the Merck Collaboration Agreement as a component of its development strategy since it will allow the Company to advance its autoimmune programs in partnership with a world class pharmaceutical company, while also continuing its focus on its more advanced cancer programs. The research program outlined in the Merck Collaboration Agreement entails (1) the Company's research, discovery and development of certain Immuno-STATTM 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.

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. Additionally, the Company may be eligible to receive 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. Excluding the up-front payment described above, the Company is 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 are achieved. The Merck Collaboration Agreement requires the Company to use the first $2.5 million milestone payment it receives under the agreement to fund contract research. The amount of the royalty payments is a percentage of product sales ranging in the single digits based on the amount of such sales.

As it relates to the Merck Collaboration Agreement, the Company recognized the upfront 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 performs 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.

On November 18, 2020, the Company entered into a First Amendment to the Merck Collaboration Agreement (the "Amendment") with Merck. Pursuant to rights granted to Merck under the Merck Collaboration Agreement, the Amendment extended the term of the research program under the Merck Collaboration Agreement for an additional year, until December 31, 2021. Under the terms of the Amendment, Merck reimbursed the Company 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 the Company. On November 18, 2020, the Company 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. The Company recognized revenue related to this milestone payment pursuant to its revenue recognition policy in relation to the performance of its obligations related to the development of Immuno-STAT drug product candidates under the arrangement.

Aside from the $300,000 milestone payment earned to date, the Company does not believe that any variable consideration should be included in the transaction price at December 31, 2020. 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 by assessing the effort and expense expended during the period. For the year ended December 31, 2021, the Company recognized approximately $2,155,000 in collaboration revenue related to this agreement. The Company did not record short and long-term research and development liabilities on its balance sheet dated December 31, 2021, as the performance obligation was met and completed. At December 31, 2021, all cash was collected to date. For the year ended December 31, 2020, the Company recognized approximately $177,000 in collaboration revenue related to this agreement and recorded short and long-term research and development liabilities on its balance sheet dated December 31, 2020 of $606,771 and $0, respectively. The research collaboration term under the Merck Collaboration Agreement expired on December 31, 2021.

Collaboration Agreement with LG Chem

On November 6, 2018, the Company entered into the “LG Chem Collaboration Agreement” with 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, dated December 18, 2019 and as amended on November 5, 2020, 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 product candidates in the LG Chem Territory.

On May 16, 2019, LG Chem paid the Company a $2.5 million milestone payment for the FDA acceptance of the 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 statements of operations and comprehensive loss.

On December 7, 2020, the Company earned a $1.25 million milestone payment on the selection of a preclinical 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 preclinical 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 statements of operations and 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.

The Company recorded short and long-term research and development liabilities on its balance sheet for the year ended December 31, 2021 of $645,344 and $0, respectively.

Aside from the $6.75 million 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, 2021. 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, 2021 and 2020, the Company recognized revenue of approximately $12,786,000 and $2,978,000, respectively, related to the LG Chem Collaboration Agreement.

Capitalization of Contract Costs

The Company considered the capitalization of contract costs under the guidance in ASC 340. 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 $907,600 as of December 31, 2021, pursuant to the Einstein License 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 upfront 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 $156,600 in capitalized license expenses related to the milestone payment received in December 2020, net of accumulated amortization of approximately $827,600. For the year ended December 31, 2021, approximately $80,000 was included in prepaid expenses and other short-term assets and $0 is included in other long-term assets. The Company recorded license fee expense under ASC 730 of $125,750 related to the $3 million milestone payment earned in November 2021.

11. 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, 2021 and 2020. 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 32,202,496 shares and 30,351,366 shares were issued and outstanding at December 31, 2021 and 2020, respectively.

12. Related Party Transactions

Information with respect to payments under the Einstein License is described in Note 7.

13. Income Taxes

The Company accounts for income taxes under the provision of ASC 740, *Income Taxes*. 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, 2021 and 2020 are as follows:

	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 45,994,000	$ 34,539,000
Research and other credits	3,708,000	2,312,000
Reserves and accruals	7,552,000	7,446,000
Other	301,000	—
Total gross deferred tax assets	57,555,000	44,297,000
Less valuation allowance	(54,782,000)	(42,321,000)
Total deferred tax assets	2,773,000	1,976,000
Deferred tax liability:		
Depreciation	(2,773,000)	(1,974,000)
Other	—	(2,000)
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, 2021, and 2020, 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, 2021 and 2020 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, 2021 and 2020 is as follows:

	Years Ended December 31,	
	2021	2020
U. S. Federal statutory tax rate	(21)%	(21)%
State Taxes	(6)%	(7)%
Change in valuation allowance	29%	30%
Tax credits	(3)%	(1)%
Stock based compensation	1%	(2)%
Tax reform	0%	0%
Foreign withholding taxes	1%	0%
Other	0%	1%
Effective tax rate	1%	0%

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, 2021 and 2020, the Company had unrecognized tax benefits related to Federal and state research tax credits of approximately $1,666,000 and $1,675,000, 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, 2021, the Company has available net operating loss carryforwards for Federal and state income tax purposes of approximately $169,072,206 and $168,618,099, respectively, which, if not utilized earlier, will begin to expire in 2035. Approximately $140,560,428 of the federal net operating losses have an indefinite carryforward. The Company has Federal research credits of approximately $4,648,000, which, if not utilized earlier, will begin to expire in 2035, and state research credits of approximately $1,309,000, which, if not utilized earlier, will begin to expire in 2031.

The following is a reconciliation of the Company's gross uncertain tax position at December 31, 2021 and 2020:

	Year Ended December 31,	
	2021	2020
Balance at the beginning of year	$ 1,675,000	$ 1,334,000
Additions for current year tax provisions	363,000	341,000
Additions for prior year tax provisions	30,000	—
Reductions of prior year tax provisions	—	—
Balance as of end of year	$ 2,068,000	$ 1,675,000

14. 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. On July 31, 2017, the Company and Einstein amended and restated the Einstein License Agreement which modified certain obligations of the parties under the Einstein License Agreement. For the years ended December 31, 2021 and 2020, the Company incurred approximately $619,000 and $75,000, 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 10.

Collaboration Agreement with LG Chem

See discussion of the LG Chem Collaboration Agreement in Note 10.

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, 2021, 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.

15. Leases

The Company is party to a multi-year, noncancelable lease agreement for its Cambridge Massachusetts-based office and lab space, approximately 19,900 square feet (the "Laboratory and Office Lease") as well as additional laboratory space (the "Additional Laboratory Lease") at the same location. The Laboratory and Office Lease includes rent escalation clauses through the lease term and a Company option to extend the lease term for up to two terms of three years each. Minimum base lease payments under the Laboratory and Office Lease are recognized on a straight-line basis over the full term of the lease. The lease term began in May 2018 and was amended last in October 2021 to extend the lease expiration date to March 14, 2024, as discussed further below.

On June 24, 2020, the Company entered into a second amendment to the Laboratory and Office Lease. Pursuant to the amendment (1) the term of the lease was extended to June 14, 2022 and (2) the monthly rental rate for the last 14 months of the lease term was increased to $375,174. The Company determined that the amendment should be accounted for as a lease modification applicable under ASC 842, not as a separate contract, with an effective date of lease modification of May 14, 2020. At the effective date of modification, the Company recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $4,826,000.

On July 20, 2020, the Company entered into a third amendment to the Additional Laboratory Lease. Pursuant to the amendment, the term of the lease was extended to June 14, 2022. The Company determined that the amendment should be accounted for as a lease modification applicable under ASC 842, not as a separate contract, with an effective date of lease modification of August 4, 2020, when the agreement was fully executed. At the effective date of modification, the Company recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $813,000.

On October 22, 2021, the Company entered into a third amendment to the Laboratory and Office Lease. Pursuant to the amendment (1) the term of the lease was extended to March 14, 2024 and (2) the monthly rental rate for the last 21 months of the lease term was increased from $375,174 to $388,000. The Company determined that the amendment should be accounted for as a lease modification applicable under ASC 842, not as a separate contract, with an effective date of lease modification of November 1, 2021, when the agreement was fully executed. At the effective date of modification, the Company recorded an adjustment to the right-of-use asset and lease liability in the amount of approximately $7,616,000.

The monthly rent payment due under the Laboratory and Office Lease is currently $375,000 until June 2022 and will increase to $388,000 for the remainder of the term.

At December 31, 2021, the Company recorded $9,809,876 to operating right-of-use asset, and $4,931,675 and $5,121,179 to short and long-term operating lease liability, respectively. At December 31, 2021, the remaining lease term was 2.29 years.

Future minimum lease payments under these leases at December 31, 2021 are as follows:

Year		
2022	$	4,931,675
2023		4,754,796
2024		1,004,739
Total lease payments		10,691,210
Less: present value discount		(638,358)
Present value of lease payments	$	10,052,853

Total rent expense of approximately $4,963,000 and $4,593,000 was included in the consolidated statements of operations and comprehensive loss for the years ended December 31, 2021 and 2020, respectively.

16. 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 did not make any contributions to the Plan during the years ended December 31, 2021 or 2020.

17. Subsequent Events

Cue Biopharma 401(k) Plan

Effective January 1, 2022, under the Cue Biopharma 401(k) Plan (the "Plan"), the Company adopted an employer contribution match of up to 3% of employee contributions. The Company will record this as an operating expense on the statement of consolidated operations in 2022 as incurred.

Lease Amendment

On January 25, 2022, the Company entered into the fourth amendment to the Additional Laboratory Lease. Pursuant to the amendment (1) the term of the lease was extended to March 14, 2024 and (2) the monthly rental rate for the amendment increased from $62,588 to $64,466 on October 15, 2022, and $66,399 on October 15, 2023.

Loan and Security Agreement

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 Term Loan Agreement provides for up to $20,000,000 in term loans to be drawn in two tranches as follows: (i) Tranche A loan of $10,000,000 and(ii) Tranche B loan of up to $10,000,000 which is available to be drawn upon meeting certain specified requirements (collectively, the "Term Loans"). The Company drew $10,000,000 in term loans on the Closing Date.

The interest rate applicable to the Term Loans is the greater of (a) the WSJ Prime Rate plus 2.25% or (b) 5.50% per annum. 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. Upon borrowing funding Tranche 2, the interest only period shall extend to December 31, 2023, followed by 24 months of amortization.

The Term Loans may be prepaid in full through February 15, 2023 with a payment of 3.00% prepayment premium, after which they may be prepaid in full through February 15, 2024 with payment of a 2.00% prepayment premium, after which they may be prepaid in full through February, 2025 with payment of a 1.00% prepayment premium, after which they may be prepaid in full with no prepayment premium. An additional final payment of 7.5% of the amount of Terms Loans advanced by the Lenders ("Exit Fee') will be due upon prepayment or repayment of the Term Loans in full.

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.

PART IV

Item 15. Exhibits, Financial Statements and 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:

			Incorporated by Reference			
Exhibit Number	**Exhibit Description**	**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	Warrant to Purchase Common Stock issued to the placement agent in the Registrant's 2015 private placement offering		S-1	4.3	09/21/17	333-220550
4.3	Form of Warrant issued to the underwriter in the Registrant's 2017 initial public offering		10-K	4.3	03/29/18	001-38327
4.4	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
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	S-1	10.10	09/21/17	333-220550
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 October 30, 2018	10-K	10.10	03/14/2019	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	License Agreement between the Registrant and MIL 21 E, LLC dated January 19, 2018	10-K	10.21	03/29/18	001-38327
10.21	First Amendment to the License Agreement between Registrant and MIL 21E, LLC dated June 18, 2018	8-K	10.1	06/20/18	001-38327
10.22	Second Amendment to License Agreement between the Registrant and MIL 21E, LLC dated June 24, 2020.	8-K	10.1	06/26/20	001-38327
10.23†	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
10.24*	Amendment No. 1 to Cue Biopharma, Inc. 2016 Omnibus Incentive Plan	10-K	10.16	03/12/2020	001-38327
10.25*	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
10.26	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

10.27	Executive Employment Agreement dated August 21, 2020 between Registrant and Kerri-Ann Millar		8-K	10.1	08/24/20	001-38327
10.28*	Consulting Agreement, dated January 1, 2017, between the Registrant and Ken Pienta, as amended by Amendment No. 1 to Consulting Agreement dated December 15, 2021	X				
10.29#	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
10.30	Third Amendment to Vivarium Agreement, dated July 20, 2020, between the Registrant and MIL 21E, LLC		10-Q	10.2	11/09/20	001-38327
10.31	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
10.32	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
10.33	Third Amendment to License Agreement, dated October 22, 2021, by and between Cue Biopharma, Inc. and MIL 21E, LLC		10-Q	10.2	11/09/21	001-38327
10.34#	Loan and Security Agreement, dated February 15, 2022, by and between Cue Biopharma, Inc. and Silicon Valley Bank	X				
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 16, 2022	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 16, 2022
/s/ Kerri-Ann Millar Kerri-Ann Millar	Chief Financial Officer (Principal Financial and Accounting Officer)	March 16, 2022
/s/ Aaron Fletcher Aaron Fletcher	Director	March 16, 2022
/s/ Cameron Gray Cameron Gray	Director	March 16, 2022
/s/ Peter A. Kiener Peter A. Kiener	Director	March 16, 2022
/s/ Frederick Driscoll Frederick Driscoll	Director	March 16, 2022
/s/ Frank Morich Frank Morich	Director	March 16, 2022
/s/ Tamar Howson Tamar Howson	Director	March 16, 2022

AMENDMENT NO. 1 TO CONSULTING AGREEMENT

THIS AMENDMENT NO. 1 TO CONSULTING AGREEMENT (this "**Amendment**"), dated as of December 15, 2021, is entered into by and between Cue Biopharma, Inc., a Delaware corporation (the "**Company**"), and Kenneth J. Pienta (the "**Consultant**"). Reference is made to that certain Consulting Agreement, dated as of January 1, 2017, by and between the Company and the Consultant (the "**Agreement**").

WHEREAS, the Company and the Consultant desire to amend the Agreement as set forth below; and

WHEREAS, Section 9 of the Agreement provides that the Agreement may be amended only by a written instrument executed by the Company and the Consultant.

NOW, THEREFORE, in consideration of the foregoing and other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, the Company and the Consultant do hereby agree with each other as follows:

1. Amendment to Section 5.1 of the Agreement. The first sentence of Section 5.1 of the Agreement is hereby amended by adding the following at the end of such sentence: "("confidential information" or "Confidential Information")."

2. Amendment to Section 6.6 of the Agreement. Section 6.6 of the Agreement is hereby amended by deleting the reference therein to "Section 5" and inserting the following in lieu thereof: "Section 6".

3. Amendment to Exhibit A of the Agreement. Exhibit A of the Agreement is hereby deleted in its entirety and the following is inserted in lieu thereof:

"SERVICES:

Consultant will serve as the Company's Interim Chief Medical Officer and will provide all services (1) requested by the Company in line with those customarily performed by a Chief Medical Officer and/or (2) required by applicable law. In the performance of such services, Consultant agrees to work approximately 40 hours per week.

COMPENSATION:

From and after the date of this Amendment, the Company will pay Consultant a fee of $475,000 annually, paid bi-weekly in arrears.

Subject to approval by the Board of Directors, you will be eligible to receive discretionary performance-based bonuses of up to 40% of your base salary per annum.

Prior to the date of this Amendment, the Company has granted Consultant options from time to time in consideration of Consultant's services. In connection with the execution of this Amendment and subject to approval by its Board of Directors, the Company will grant, pursuant to its 2016 Omnibus Incentive Plan (the "**Plan**"), Consultant an option to purchase 80,000 shares of the Company's common stock, which option will vest over two years in equal, semi-annual installments beginning six months from the date of grant, subject to the terms and conditions of the Plan and the applicable Award Agreement (as defined in the Plan)."

4. Entire Agreement. The Agreement, as amended by this Amendment, constitutes the entire agreement between the parties and, except as expressly provided herein or therein, supersedes all prior agreements and

understandings, whether written or oral, relating to the subject matter of the Agreement.

5. Effectiveness. Upon the effectiveness of this Amendment, on and after the date hereof, each reference in the Agreement to "this Agreement," "hereunder," "hereof," "herein" or words of like import, and each reference in the other documents entered into in connection with the Agreement, shall mean and be a reference to the Agreement, as amended hereby. Except as specifically amended above, the Agreement shall remain in full force and effect and is hereby ratified and confirmed.

6. Governing Law. This Amendment will be construed, interpreted and enforced in accordance with the laws of the Commonwealth of Massachusetts.

7. Counterparts. This Amendment may be executed in counterparts, each of which shall be deemed an original, but all of which shall constitute one and the same instrument.

IN WITNESS WHEREOF, the parties have executed this Amendment as of the date first above written.

CUE BIOPHARMA, INC.

By: /s/ Daniel Passeri
Name: Daniel Passeri
Title: Chief Executive Officer

CONSULTANT:

/s/ Kenneth J. Pienta
Name: Kenneth J. Pienta

Exhibit 10.34

Certain identified information has been excluded from the exhibit because it is both (i) not material and (ii) is the type of information that the registrant treats as private or confidential. Double asterisks denote omissions.

LOAN AND SECURITY AGREEMENT

THIS LOAN AND SECURITY AGREEMENT (this "Agreement") is dated as of the Effective Date between **SILICON VALLEY BANK**, a California corporation ("**Bank**"), and the borrower listed on Schedule I hereto ("**Borrower**"). The parties agree as follows:

1 LOAN AND TERMS OF PAYMENT

1.1 Term Loan.

(a) Availability. Subject to the terms and conditions of this Agreement, on or about the Effective Date, Borrower shall request and Bank shall make one (1) term loan advance in an original principal amount equal to the Term A Loan Availability Amount (the "**Term A Loan Advance**"). Subject to the terms and conditions of this Agreement, upon Borrower's request, during the Draw Period, Bank shall make up to two (2) term loan advances in an aggregate principal amount not to exceed the Term B Loan Availability Amount (each a "**Term B Loan Advance**", and collectively, the "**Term B Loan Advances**"). The Term A Loan Advance and the Term B Loan Advances are each referred to herein as a "**Term Loan Advance**" and, collectively, as the "**Term Loan Advances**". Borrower may request Term Loan Advances as set forth on Schedule I hereto.

(b) Repayment. Borrower shall repay each Term Loan Advance as set forth in Schedule I hereto. All outstanding principal and accrued and unpaid interest under each Term Loan Advance, and all other outstanding Obligations with respect to such Term Loan Advance, are due and payable in full on the Term Loan Maturity Date.

(c) Permitted Prepayment. Borrower shall have the option to prepay all, but not less than all, of the Term Loan Advances, provided Borrower (i) delivers written notice to Bank of its election to prepay the Term Loan Advances at least five (5) Business Days prior to such prepayment, and (ii) pays, on the date of such prepayment (A) the outstanding principal plus accrued and unpaid interest with respect to the Term Loan Advances, (B) the Final Payment, (C) the Prepayment Fee, and (D) all other sums, if any, that shall have become due and payable with respect to the Term Loan Advances, including interest at the Default Rate with respect to any past due amounts.

(d) Mandatory Prepayment Upon an Acceleration. If the Term Loan Advances are accelerated by Bank following the occurrence and during the continuance of an Event of Default, Borrower shall immediately pay to Bank an amount equal to the sum of (i) all outstanding principal plus accrued and unpaid interest with respect to the Term Loan Advances, (ii) the Final Payment, (iii) the Prepayment Fee, and (iv) all other sums, if any, that shall have become due and payable with respect to the Term Loan Advances, including interest at the Default Rate with respect to any past due amounts.

1.2 Payment of Interest on the Credit Extensions.

(a) Interest Payments. Interest on the principal amount of each Term Loan Advance is payable as set forth on Schedule I hereto.

(b) Interest Rate.

(i) Term Loan Advances. Subject to Section 1.2(c), the outstanding principal amount of any Term Loan Advance shall accrue interest as set forth on Schedule I hereto.

(ii) All-In Rate. Notwithstanding any terms in this Agreement to the contrary, if at any time the interest rate applicable to any Obligations is less than zero percent (0.0%), such interest rate shall be deemed to be zero percent (0.0%) for all purposes of this Agreement.

(c) Default Rate. Immediately upon the occurrence and during the continuance of an Event of Default, the outstanding Obligations shall bear interest at a rate per annum which is three percent (3.0%) the rate that is otherwise applicable thereto (the "**Default Rate**"), unless Bank otherwise elects, in its sole discretion to impose a lesser increase or no increase. Fees and expenses which are required to be paid by Borrower pursuant to the Loan Documents (including, without limitation, Bank Expenses) but are not paid when due shall bear interest until paid at a rate equal to the highest rate applicable to the Obligations. Payment or acceptance of the increased interest rate provided in this Section 1.2(c) is not a permitted alternative to timely payment and shall not constitute a waiver of any Event of Default or otherwise prejudice or limit any rights or remedies of Bank.

(d) Adjustment to Interest Rate. Each change in the interest rate applicable to any amounts payable under the Loan Documents based on changes to the Prime Rate shall be effective on the effective date of any change to the Prime Rate and to the extent of such change.

(e) Interest Computation. Interest shall be computed as set forth on Schedule I hereto. In computing interest, the date of the making of any Credit Extension shall be included and the date of payment shall be excluded; provided, however, that if any Credit Extension is repaid on the same day on which it is made, such day shall be included in computing interest on such Credit Extension.

1.3 Fees. Borrower shall pay to Bank:

(a) Final Payment. The Final Payment, when due hereunder, which shall be fully earned and non-refundable as of such date;

(b) Prepayment Fee. The Prepayment Fee, when due hereunder, which shall be fully earned and non-refundable as of such date;

(c) Bank Expenses. All Bank Expenses incurred through and after the Effective Date, when due (or, if no stated due date, upon demand by Bank); and

(d) Good Faith Deposit. Borrower has paid a deposit of $75,000.00 (the "**Good Faith Deposit**") prior to the date hereof, which shall be applied towards Bank Expenses incurred through the Effective Date. Any portion of the Good Faith Deposit not utilized to pay Bank Expenses through the Effective Date will be deposited into Borrower's Designated Deposit Account.

Unless otherwise provided in this Agreement or in a separate writing by Bank, Borrower shall not be entitled to any credit, rebate, or repayment of any fees earned by Bank pursuant to this Agreement, notwithstanding any termination of this Agreement or the suspension or termination of Bank's obligation to make loans and advances hereunder. Bank may deduct amounts owing by Borrower under the clauses of this Section 1.3 pursuant to the terms of Section 1.4(c). Bank shall provide Borrower written notice of deductions made pursuant to the terms of the clauses of this Section 1.3.

1.4 Payments; Application of Payments; Debit of Accounts.

(a) All payments (including prepayments) to be made by Borrower under any Loan Document shall be made in immediately available funds in Dollars, without setoff, counterclaim, or deduction, before 12:00 p.m. Eastern time on the date when due. Payments of principal and/or interest received after 12:00 p.m. Eastern time are considered received at the opening of business on the next Business Day. When a payment is due on a day that is not a Business Day, the payment shall be due the next Business Day, and additional fees or interest, as applicable, shall continue to accrue until paid.

(b) Bank has the exclusive right to determine the order and manner in which all payments with respect to the Obligations may be applied. Borrower shall have no right to specify the order or the accounts to which Bank shall allocate or apply any payments required to be made by Borrower to Bank or otherwise received by Bank under this Agreement when any such allocation or application is not specified elsewhere in this Agreement.

(c) Bank may debit any of Borrower's deposit accounts maintained with Bank, including the Designated Deposit Account, for principal and interest payments or any other amounts Borrower owes Bank when due under the Loan Documents. These debits shall not constitute a set-off.

1.5 Change in Circumstances.

(a) Increased Costs. If any Change in Law shall: (i) impose, modify, or deem applicable any reserve, special deposit, compulsory loan, insurance charge, or similar requirement against assets of, deposits with or for the account of, or advances, loans, or other credit extended or participated in by, Bank, (ii) subject Bank to any Taxes (other than (A) Indemnified Taxes, (B) Taxes described in clauses (b) through (d) of the definition of Excluded Taxes, and (C) Connection Income Taxes) on its loans, loan principal, letters of credit, commitment, or other obligations, or its deposits, reserves, other liabilities, or capital attributable thereto, or (iii) impose on Bank any other condition, cost, or expense (other than Taxes) affecting this Agreement or Credit Extensions made by Bank, and the result of any of the foregoing shall be to increase the cost to Bank of making, converting to, continuing, or maintaining any Credit Extension (or of maintaining its obligation to make any such Credit Extension), or to reduce the amount of any sum received or receivable by Bank hereunder (whether of principal, interest, or any other amount) then, upon written request of Bank, Borrower shall promptly pay to Bank such additional amount or amounts as will compensate Bank for such additional costs incurred or reduction suffered.

(b) Capital Requirements. If Bank determines that any Change in Law affecting Bank regarding capital or liquidity requirements, has or would have the effect of reducing the rate of return on Bank's capital as a consequence of this Agreement or the Credit Extensions made by Bank to a level below that which Bank could have achieved but for such Change in Law (taking into consideration Bank's policies with respect to capital adequacy and liquidity), then from time to time upon written request of Bank, Borrower shall promptly pay to Bank such additional amount or amounts as will compensate Bank for any such reduction suffered.

(c) Delay in Requests. Failure or delay on the part of Bank to demand compensation pursuant to this Section 1.5 shall not constitute a waiver of Bank's right to demand such compensation; provided that Borrower shall not be required to compensate Bank pursuant to subsection (a) for any increased costs incurred or reductions suffered more than nine (9) months prior to the date that Bank notifies Borrower of the Change in Law giving rise to such increased costs or reductions (except that if the Change in Law giving rise to such increased costs or reductions is retroactive, then the nine (9)-month period shall be extended to include the period of retroactive effect).

1.6 Taxes.

(a) Payments Free of Taxes. Any and all payments by or on account of any obligation of Borrower under any Loan Document shall be made without deduction or withholding for any Taxes, except as required by Applicable Law. If any Applicable Law (as determined in the good-faith discretion of Borrower) requires the deduction or withholding of any Tax from any such payment by Borrower, then (i) Borrower shall be entitled to make such deduction or withholding, (ii) Borrower shall timely pay the full amount deducted or withheld to the relevant Governmental Authority in accordance with Applicable Law, and (iii) if such Tax is an Indemnified Tax, the sum payable by Borrower shall be increased as necessary so that, after such deduction or withholding has been made (including such deductions and withholdings applicable to additional sums payable under this Section 1.6), Bank receives an amount equal to the sum it would have received had no such deduction or withholding been made.

(b) Payment of Other Taxes by Borrower. Without limiting the provisions of subsection (a) above, Borrower shall timely pay any Other Taxes to the relevant Governmental Authority in accordance with Applicable Law.

(c) Tax Indemnification. Without limiting the provisions of subsections (a) and (b) above, Borrower shall, and does hereby, indemnify Bank, within ten (10) days after demand therefor, for the full amount of any Indemnified Taxes (including Indemnified Taxes imposed or asserted on or attributable to amounts payable under this Section 1.6) payable or paid by Bank or required to be withheld or deducted from a payment to Bank and any reasonable expenses arising therefrom or with respect thereto, whether or not such Indemnified Taxes were correctly or legally imposed or asserted by the relevant Governmental Authority. A reasonably detailed certificate as to the amount of such payment or liability delivered to Borrower by Bank shall be conclusive absent manifest error.

(d) Evidence of Payments. As soon as practicable after any payment of Taxes by Borrower to a Governmental Authority pursuant to this Section 1.6, Borrower shall deliver to Bank a certified copy of a receipt issued by such Governmental Authority evidencing such payment, a copy of the return reporting such payment, or other evidence of such payment reasonably satisfactory to Bank.

(e) Status of Bank. If Bank (including any assignee or successor) is entitled to an exemption from or reduction of withholding tax with respect to payments made under any Loan Document, Bank shall deliver to Borrower, at the time or times reasonably requested by Borrower, such properly completed and executed documentation reasonably requested by Borrower as will permit such payments to be made without withholding or at a reduced rate of withholding. In addition, Bank, if reasonably requested by Borrower, shall deliver such other documentation prescribed by Applicable Law or reasonably requested by Borrower as will enable Borrower to determine whether or not Bank is subject to backup withholding or information reporting requirements. Without limiting the generality of the foregoing, Bank shall deliver whichever of IRS Form W-9, IRS Form W-8BEN-E, IRS Form W-8ECI or W-8IMY is applicable, as well as any applicable supporting documentation or certifications.

1.7 Procedures for Borrowing.

(a) Subject to the prior satisfaction of all other applicable conditions to the making of a Term Loan Advance set forth in this Agreement (which must be satisfied no later than 12:00 p.m. Eastern time on the applicable Funding Date), to obtain a Term Loan Advance, Borrower shall notify Bank (which notice shall be irrevocable) by 12:00 p.m. Eastern time at least 2 Business Days prior to the proposed Funding Date of the Term Loan Advance. Such notice shall be made by electronic mail or by telephone and, together with any such notification, Borrower shall deliver to Bank by electronic mail a completed Payment/Advance Form executed by an Authorized Signer and such other reports and information as Bank may reasonably request. Bank may rely on any telephone notice given by a person whom Bank reasonably believes is an Authorized Signer. Borrower will indemnify Bank for any loss Bank suffers due to such belief or reliance. Bank shall have received satisfactory evidence that the Board has approved that such Authorized Signer may provide such notices and request such Term Loan Advance (which requirement may be deemed satisfied by the prior delivery of Borrowing Resolutions or a secretary's certificate that certifies as to such Board approval).

(b) Bank shall credit proceeds of a Credit Extension to the Designated Deposit Account. Bank may make Term Loan Advances under this Agreement based on instructions from an Authorized Signer.

2 CONDITIONS OF CREDIT EXTENSIONS

2.1 Conditions Precedent to Initial Credit Extension. Bank's obligation to make the initial Credit Extension is subject to the condition precedent that Bank shall have received, in form and substance satisfactory to Bank, such documents, and completion of such other matters, as Bank shall have reasonably requested, including, without limitation:

(a) duly executed Loan Documents;

(b) the Operating Documents of Borrower and (i) a long-form good standing certificate of Borrower certified by the Secretary of State of the State of Delaware and (ii) a good standing/foreign qualification certificate certified by the Secretary of State of the Commonwealth of Massachusetts, in the case of (i) and (ii), each as of a date no earlier than 30 days prior to the Effective Date;

(c) certificate duly executed by a Responsible Officer or secretary of Borrower with respect to Borrower's (i) Operating Documents and (ii) Borrowing Resolutions;

(d) certified copies, dated as of a recent date, of searches for financing statement filed in the central filing office of the State of Delaware, accompanied by written evidence (including any UCC termination statements) that the Liens indicated in any such financing statements either constitute Permitted Liens or have been or, in connection with the initial Credit Extension, will be terminated or released;

(e) duly executed Perfection Certificate of Borrower;

(f) duly executed signature to the Stock Pledge Agreement;

(g) stock power forms (5 originals) executed by Borrower with respect to capital stock of Securities Corp. and delivery of stock certificates evidencing ownership interest in Securities Corp.;

(h) duly executed landlord's consent in favor of Bank for Borrower's leased location at 21 Erie Street, Cambridge, Massachusetts 02139 by the landlord thereof;

(i) duly executed bailee's waiver in favor of Bank for each location where Borrower maintains property with a third party, by each such third party;

(j) a legal opinion of Borrower's counsel dated as of the Effective Date;

(k) evidence satisfactory to Bank that the insurance policies and endorsements required by Section 5.6 hereof are in full force and effect, together with appropriate evidence showing lender loss payable and additional insured clauses or endorsements in favor of Bank; and

(l) payment of the fees and Bank Expenses then due as specified in Section 1.3 hereof.

2.2 Conditions Precedent to all Credit Extensions. Bank's obligation to make each Credit Extension, including the initial Credit Extension, is subject to the following conditions precedent:

(a) receipt of Borrower's Credit Extension request and the related materials and documents as required by and in accordance with Section 1.7;

(b) the representations and warranties in this Agreement shall be true and correct in all material respects as of the date of any Credit Extension request and as of the Funding Date of each Credit Extension; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true and correct in all material respects as of such date, and no Default or Event of Default shall have occurred and be continuing or result from the Credit Extension. Each Credit Extension is Borrower's representation and warranty on that date that the representations and warranties in this Agreement remain true and correct in all material respects; provided, however, that such materiality qualifier shall not be applicable to any representations and warranties that already are qualified or modified by materiality in the text thereof; and provided, further that those representations and warranties expressly referring to a specific date shall be true and correct in all material respects as of such date; and

(c) a Material Adverse Change shall not have occurred and be continuing.

2.3 Covenant to Deliver. Borrower shall deliver to Bank each item required to be delivered to Bank under this Agreement as a condition precedent to any Credit Extension. A Credit Extension made prior to the receipt by Bank of any such item shall not constitute a waiver by Bank of Borrower's obligation to deliver such item, and the making of any Credit Extension in the absence of a required item shall be in Bank's sole discretion.

3 <u>CREATION OF SECURITY INTEREST</u>

3.1 Grant of Security Interest.

(a) Borrower hereby grants Bank, to secure the payment and performance in full of all of the Obligations, a continuing security interest in, and pledges to Bank, the Collateral, wherever located, whether now owned or hereafter acquired or arising, and all proceeds and products thereof.

(b) Borrower acknowledges that it previously has entered, or may in the future enter, into Bank Services Agreements with Bank. Regardless of the terms of any Bank Services Agreement, Borrower agrees that any amounts Borrower owes Bank thereunder shall be deemed to be Obligations hereunder and that it is the intent of Borrower and Bank to have all such Obligations secured by the first priority perfected security interest in the Collateral granted herein (subject to Permitted Liens).

3.2 Authorization to File Financing Statements. Borrower hereby authorizes Bank to file financing statements, without notice to Borrower, with all jurisdictions deemed necessary or appropriate by Bank to perfect or protect Bank's interest or rights hereunder, including a notice that any disposition of the Collateral, by Borrower or any other Person, shall be deemed to violate the rights of Bank under the Code. Such financing statements may indicate the Collateral as "all assets of the Debtor" or words of similar effect.

3.3 Termination. If this Agreement is terminated, Bank's Lien in the Collateral shall continue until the Obligations (other than inchoate indemnity obligations, any obligations which by their terms, are to survive the termination of this Agreement, and any Obligations under Bank Services Agreements that are cash collateralized in accordance with Section 3.3) are repaid in full in cash. Upon payment in full in cash of the Obligations (other than inchoate indemnity obligations, any obligations which by their terms, are to survive the termination of this Agreement, and any Obligations under Bank Services Agreements that are cash collateralized in accordance with Section 3.3) and at such time as Bank's obligation to make Credit Extensions has terminated, Bank shall, at Borrower's sole cost and expense, terminate its security interest in the Collateral and all rights therein shall revert to Borrower. In the event (a) all Obligations (other than inchoate indemnity obligations and any obligations which, by their terms are to survive termination of this Agreement), except for Bank Services, are satisfied in full, and (b) this Agreement is terminated, Bank shall terminate the security interest granted herein upon Borrower providing cash collateral acceptable to Bank in its sole discretion for Bank Services, if any. In the event such Bank Services consist of outstanding Letters of Credit, Borrower shall provide to Bank cash collateral in an amount equal to at least (x) 105.0% of the face amount of all such Letters of Credit denominated in Dollars and (y) 110.0% of the Dollar Equivalent of the face amount of all such Letters of Credit denominated in a Foreign Currency, plus, in each case, all interest, fees, and costs due or estimated by Bank to become due in connection therewith, to secure all of the Obligations relating to such Letters of Credit.

3.4 Release of Collateral. Bank hereby agrees that any Liens granted to Bank by Borrower or any of its Subsidiaries on any Collateral shall be automatically released (a) in accordance with Section 3.3, upon the satisfaction in full, in cash, of the Obligations and termination of this Agreement (other than inchoate indemnity obligations, any obligations which by their terms, are to survive the termination of this Agreement, and any Obligations under Bank Services Agreements that are cash collateralized in accordance with Section 3.3), or (b) if such Collateral is sold, transferred or otherwise disposed of by Borrower or any of its Subsidiaries pursuant to any sale, transfer or other disposition that is made in compliance with, and subject to the terms and condition of, this Agreement. Any such release shall not in any manner discharge, affect, or impair the Obligations or any Liens (other than those expressly being released) upon (or obligations of Borrower or any of its Subsidiaries in respect of) all interests retained by Bank in Borrower or any of its Subsidiaries. Upon Borrower's reasonable request and at Borrower's sole cost and expense, Bank shall execute, deliver or authorize such documents as may be reasonably required to evidence any release described above.

4 REPRESENTATIONS AND WARRANTIES

Borrower represents and warrants as follows:

4.1 Due Organization, Authorization; Power and Authority.

(a) Borrower and each of its Subsidiaries are each duly existing and in good standing as a Registered Organization in their respective jurisdiction of formation and are qualified and licensed to do business and are in good standing in any jurisdiction in which the conduct of their respective business or their ownership of property requires that they be qualified, except where the failure to do so could not reasonably be expected to have a material adverse effect on Borrower's business or operations.

(b) All information set forth on the Perfection Certificate (as updated from time to time) pertaining to Borrower and each of its Subsidiaries is true and correct in all material respects (it being understood and agreed that Borrower may from time to time update certain information in the Perfection Certificate after the Effective Date to the extent permitted by one or more specific provisions in this Agreement and the Perfection Certificate shall be deemed to be updated to the extent such notice is provided to Bank of such permitted update).

(c) The execution, delivery, and performance by Borrower and each of its Subsidiaries of the Loan Documents to which they are parties have been duly authorized, and do not (i) conflict with any of Borrower's or any such Subsidiary's organizational documents, (ii) contravene, conflict with, constitute a default under, or violate any material Applicable Law, (iii) contravene, conflict with, or violate any applicable order, writ, judgment, injunction, decree, determination or award of any Governmental Authority by which Borrower or any of its Subsidiaries or any of their property or assets may be bound or affected, (iv) require any action by, filing (other than financing statements), registration, or qualification with, or Governmental Approval from, any Governmental Authority (except such Governmental Approvals which have already been obtained and are in full force and effect), or (v) conflict with, contravene, constitute a default or breach under, or result in or permit the termination or acceleration of, any material agreement by which Borrower or any of its Subsidiaries is bound. Neither Borrower nor any of its Subsidiaries are in default under any agreement to which they are parties or by which it is bound in which the default could reasonably be expected to have a material adverse effect on Borrower's or any of its Subsidiary's business or operations.

4.2 Collateral.

(a) The security interest granted herein is and shall at all times continue to be a first priority perfected security interest in the Collateral (subject to Permitted Liens). Borrower has good title to, rights in, and the power to transfer each item of the Collateral upon which it purports to grant a Lien hereunder, free and clear of any and all Liens except Permitted Liens.

(b) Borrower has no Collateral Accounts at or with any bank or financial institution other than Bank or Bank's Affiliates except for the Collateral Accounts described in the Perfection Certificate delivered to Bank in connection herewith and which Borrower has taken such actions as are necessary to give Bank a perfected security interest therein, pursuant to the terms of Section 5.7(c). The Accounts are bona fide, existing obligations of the Account Debtors.

(c) The Collateral (other than Collateral (i) in the possession of employees of Borrower or its Subsidiaries, (ii) in transit, or (iii) with an aggregate value of less than $100,000.00) is not in the possession of any third-party bailee (such as a warehouse) except as otherwise provided in the Perfection Certificate or as permitted pursuant to Section 6.2. None of the components of the Collateral (other than Collateral (i) in the possession of employees of Borrower or its Subsidiaries, (ii) in transit, or (iii) with an aggregate value of less than $100,000.00) shall be maintained at locations other than as provided in the Perfection Certificate or as permitted pursuant to Section 6.2.

(d) All Inventory is in all material respects of good and marketable quality, free from material defects.

(e) Borrower owns, or possesses the right to use to the extent necessary in its business, all Intellectual Property, licenses, and other intangible assets that are used in the conduct of its business as now operated, except to the extent that such failure to own or possess the right to use such asset would not reasonably be expected to have a material adverse effect on Borrower's business or operations, and no such asset, to the best knowledge of Borrower, conflicts with the valid Intellectual Property of any other Person to the extent that such conflict could reasonably be expected to have a material adverse effect on Borrower's business or operations.

(f) Except as noted on the Perfection Certificate or for which notice has been given to Bank pursuant to and in accordance with Section 5.8(b), Borrower is not a party to, nor is it bound by, any Restricted License.

4.3 Litigation. Other than as set forth in the Perfection Certificate or as disclosed to Bank pursuant to Section 5.3(j), there are no actions, investigations or proceedings pending or, to the knowledge of any Responsible Officer, threatened in writing by or against Borrower or any of its Subsidiaries involving more than, individually or in the aggregate, $100,000.00 not covered by independent third party insurance as to which liability has been accepted by the carrier providing such insurance.

4.4 Financial Statements; Financial Condition. All consolidated financial statements for Borrower and any of its Subsidiaries delivered to Bank by submission to the Financial Statement Repository or otherwise submitted to Bank fairly present in all material respects Borrower's consolidated financial condition and Borrower's consolidated results of operations for the periods covered thereby, subject, in the case of unaudited financial statements, to normal year-end adjustments and the absence of footnote disclosures. There has not been any material deterioration in Borrower's consolidated financial condition since the date of the most recent financial statements submitted to the Financial Statement Repository or otherwise submitted to Bank.

4.5 Solvency. The fair salable value of Borrower's consolidated assets (including goodwill minus disposition costs) exceeds the fair value of Borrower's liabilities; Borrower is not left with unreasonably small capital after the transactions in this Agreement; and Borrower and each of its Subsidiaries are able to pay their debts (including trade debts) as they mature.

4.6 Regulatory Compliance. Borrower is not an "investment company" or a company "controlled" by an "investment company" under the Investment Company Act of 1940, as amended. Borrower is not engaged as one of its important activities in extending credit for margin stock (under Regulations X, T and U of the Federal Reserve Board of Governors). Borrower and each of its Subsidiaries (a) have complied in all material respects with all Applicable Law, and (b) have not violated any Applicable Law the violation of which could reasonably be expected to have a material adverse effect on Borrower's business or operations. Borrower and each of its Subsidiaries have duly complied with, and their respective facilities, business, assets, property, leaseholds, real property and Equipment are in compliance with, Environmental Laws, except where the failure to do so could not reasonably be expected to have a material adverse effect on Borrower's business or operations; and there have been no outstanding citations, notices or orders of non-compliance issued to Borrower or any of its Subsidiaries or relating to their respective facilities, businesses, assets, property, leaseholds, real property or Equipment under such Environmental Laws, which could reasonably expected to have a material adverse effect on Borrower's business or operations. Borrower and each of its Subsidiaries have obtained all consents, approvals and authorizations of, made all declarations or filings with, and given all notices to, all Governmental Authorities that are necessary to continue their respective businesses as currently conducted, except where the failure to obtain or make or file the same would not reasonably be expected to have a material adverse effect on Borrower's business or operations.

4.7 Subsidiaries; Investments. Borrower does not own any stock, partnership, or other ownership interest or other equity securities except for Permitted Investments.

4.8 Tax Returns and Payments; Pension Contributions.

(a) Borrower and each of its Subsidiaries have timely filed, or submitted extensions for, all required tax returns and reports, and Borrower and each of its Subsidiaries have timely paid all foreign, federal, state and local taxes, assessments, deposits, and contributions owed by Borrower and each of its Subsidiaries except (a) to the extent such taxes are being contested in good faith by appropriate proceedings promptly instituted and diligently conducted, so long as such reserve or other appropriate provision, if any, as shall be required in conformity with GAAP shall have been made therefor, or (b) if such taxes, assessments, deposits, and contributions do not, individually or in the aggregate, exceed $20,000.00. Borrower is unaware of any claims or adjustments proposed for any of Borrower's or any of its Subsidiary's prior tax years which could result in additional taxes becoming due and payable by Borrower or any of its Subsidiaries in excess of $20,000.00 in the aggregate.

(b) If, and to the extent applicable, Borrower and each of its Subsidiaries have paid all amounts necessary to fund all present pension, profit sharing, and deferred compensation plans in accordance with their terms, and neither Borrower nor any of its Subsidiaries has withdrawn from participation in, and has not permitted partial or complete termination of, or permitted the occurrence of any other event with respect to, any such plan which could reasonably be expected to result in any liability of Borrower or any of its Subsidiaries, including any liability to the Pension Benefit Guaranty Corporation or its successors or any other Governmental Authority.

4.9 Full Disclosure. No written representation, warranty, or other statement of Borrower or any of its Subsidiaries in any report, certificate, or written statement submitted to the Financial Statement Repository or otherwise submitted to Bank in connection with the Loan Documents, as of the date such representation, warranty, or other statement was made, taken together with all such reports, certificates, and written statements submitted to the Financial Statement Repository or otherwise submitted to Bank in connection with the Loan Documents, contains any untrue statement of a material fact or omits to state a material fact necessary to make the statements contained in the reports, certificates, or written statements not misleading in light of the circumstances under which they were made (it being recognized by Bank that the projections and forecasts provided by Borrower or any of its Subsidiaries in good faith and based upon reasonable assumptions are not viewed as facts and that actual results during the period or periods covered by such projections and forecasts may differ from the projected or forecasted results).

4.10 Sanctions. Neither Borrower nor any of its Subsidiaries is: (a) in violation of any Sanctions; or (b) a Sanctioned Person. Neither Borrower nor any of its Subsidiaries, directors or officers, or, to the knowledge of Borrower or its Subsidiaries, any of Borrower's or its Subsidiaries' employees, agents, or Affiliates: (i) conducts any business or engages in any transaction or dealing with any Sanctioned Person, including making or receiving any contribution of funds, goods, or services to or for the benefit of any Sanctioned Person; (ii) deals in, or otherwise engages in any transaction relating to, any property or interests in property blocked pursuant to any Sanctions; (iii) engages in or conspires to engage in any transaction that evades or avoids, or has the purpose of evading or avoiding, or attempts to violate, any of the prohibitions set forth in any Sanctions; or (iv) otherwise engages in any transaction that could cause Bank to violate any Sanctions.

4.11 Healthcare Permits. (a) Borrower and each of its Subsidiaries have obtained all Healthcare Permits and other rights from, and have made all declarations and filings with, all applicable Governmental Authorities, all self-regulatory authorities and all courts and other tribunals necessary to engage in the management and/or operation of their respective businesses; (b) each such Healthcare Permit is valid and in full force and effect, and Borrower and each of its Subsidiaries are in compliance with the terms and conditions of all such Healthcare Permits; and (c) neither Borrower nor any of its Subsidiaries has received notice from any Governmental Authority with respect to the revocation, suspension, restriction, limitation or termination of any Healthcare Permit nor, to the knowledge of Borrower or any of its Subsidiaries, is any such action proposed or threatened in writing.

4.12 Compliance with Healthcare Laws.

(a) Borrower is in compliance with all applicable Healthcare Laws. Without limiting the generality of the foregoing, Borrower has not received written notice by a Governmental Authority of any violation (or of any investigation, audit, or other proceeding involving allegations of any violation) of any Healthcare Laws, and no investigation, inspection, audit or other proceeding involving allegations of any violation is, to the knowledge of Borrower, threatened in writing or contemplated.

(b) To the knowledge of Borrower, Borrower is not in default or violation of any law which is applicable to Borrower or its respective assets or the conduct of its respective businesses and Borrower has not been debarred or excluded from participation under a state or federal health care program, including any state or federal workers compensation program.

(c) Borrower is not a party to any corporate integrity agreements, deferred prosecution agreements, monitoring agreements, consent decrees, settlement orders or similar agreements with or imposed by any Governmental Authority.

5 AFFIRMATIVE COVENANTS

Borrower shall do all of the following:

5.1 Use of Proceeds. Cause the proceeds of the Credit Extensions to be used solely (a) as working capital or (b) to fund its general business purposes, and not for personal, family, household or agricultural purposes.

5.2 Government Compliance.

(a) Maintain its and all of its Subsidiaries' legal existence (except as permitted under Section 6.3 with respect to Subsidiaries only) and good standing in their respective jurisdictions of formation and maintain qualification in each jurisdiction in which the failure to so qualify would reasonably be expected to have a material adverse effect on Borrower's business or operations. Borrower shall comply, and have each Subsidiary comply, in all material respects, with all laws, ordinances and regulations to which it is subject.

(b) Obtain all of the Governmental Approvals necessary for the performance by Borrower and each of its Subsidiaries of their obligations under the Loan Documents to which they are parties, including any grant of a security interest to Bank. Borrower shall promptly provide copies of any such obtained Governmental Approvals to Bank.

(c) Cause the operations and property of Borrower, each of its Subsidiaries, to comply with all applicable Healthcare Laws. Without limiting the foregoing, the operations and property of Borrower and each of its Subsidiaries shall comply with HIPAA in all material respects. Borrower has established and maintains a corporate compliance program that (i) addresses the material Requirements of Law, including all applicable Healthcare Laws, of Governmental Authorities having jurisdiction over its business and operations, and (ii) has been structured to account for the guidance issued by the U.S. Department of Health and Human Services regarding characteristics of effective corporate compliance programs. As of the Effective Date, Borrower has delivered to Bank an accurate and complete copy of each material report, study, survey or other document of which Borrower has knowledge that addresses or otherwise relates to the compliance by Borrower and each of its Subsidiaries, with applicable Healthcare Laws.

5.3 Financial Statements, Reports. Deliver to Bank by submitting to the Financial Statement Repository:

(a) Monthly Financial Statements. As soon as available, but no later than 30 days after the last day of each month (except the months ending March 31, June 30, September 30, and December 31), a company prepared consolidated balance sheet and income statement covering Borrower's consolidated operations for such month and in a form reasonably acceptable to Bank;

(b) Monthly Compliance Statement. Within 30 days after the last day of each month (except the months ending March 31, June 30, September 30, and December 31) and together with the statements set forth in Section 5.3(a), a duly completed Compliance Statement, confirming that as of the end of such month, Borrower was in full compliance with all of the terms and conditions of this Agreement, and setting forth calculations showing compliance with the financial covenants set forth in this Agreement (if any) and such other information as Bank may reasonably request;

(c) Quarterly Compliance Statement. Within 45 days after the last day of each fiscal quarter (except within 90 days following the end of each fiscal quarter ending December 31) and together with the statements set forth in Section 5.3(d), a duly completed Compliance Statement, confirming that, as of the end of such fiscal quarter, Borrower was in full compliance with all of the terms and conditions of this Agreement, and setting forth calculations showing compliance with the financial covenants set forth in this Agreement (if any), and such other information as Bank may reasonably request;

(d) 10-Q reports. Within 45 days after the end of the first three fiscal quarters of Borrower, a company prepared consolidated balance sheet and income statement covering Borrower's consolidated operations for such quarter, consistent with such quarterly financial statements submitted to the SEC, in a form acceptable to Bank;

(e) Annual Operating Budget and Financial Projections. As soon as available, and in any event within 30 days after the last day of each fiscal year of Borrower, and contemporaneously with any updates or amendments thereto, (A) annual operating budgets (including income statements, balance sheets and cash flow statements, by month) for the current fiscal year of Borrower, and (B) annual financial projections for the current fiscal year (on a quarterly basis), in each case as approved by the Board, together with any related business forecasts used in the preparation of such annual financial projections;

(f) 10-K Reports and Annual Audited Financial Statements. As soon as available, and in any event within 90 days following the end of Borrower's fiscal year, Borrower's 10-K report, together with audited consolidated financial statements prepared under GAAP, consistently applied, together with an unqualified opinion on the financial statements from an independent certified public accounting firm reasonably acceptable to Bank;

(g) SEC Filings. To the extent that Borrower or any of its Subsidiaries is or becomes subject to the reporting requirements under the Exchange Act within five (5) days following filing, notification of the filing and copies of all periodic and other reports, proxy statements and other materials filed by Borrower and/or any of its Subsidiaries or any Guarantor with the SEC, any Governmental Authority succeeding to any or all of the functions of the SEC, or with any national securities exchange, or distributed to its shareholders, as the case may be. Documents required to be delivered pursuant to the terms hereof (to the extent any such documents are included in materials otherwise filed with the SEC) may be delivered electronically and if so delivered, shall be deemed to have been delivered on the date on which Borrower or any of its Subsidiaries posts such documents, or provides a link thereto, on Borrower's or any of its Subsidiaries' website on the internet at Borrower's or any of its Subsidiaries' website address;

(h) Security Holder and Subordinated Debt Holder Reports. Within five (5) days of delivery, copies of all statements, reports, and notices made available to Borrower's security holders or to any holders of Subordinated Debt (solely in their capacities as security holders or holders of Subordinated Debt and not in any other role);

(i) Beneficial Ownership Information. If applicable to Borrower, upon request by Bank, prompt written notice of any changes to the beneficial ownership information set out in Section 14 of the Perfection Certificate. Borrower understands and acknowledges that Bank relies on such true, accurate, and up-to-date beneficial ownership information to meet Bank's regulatory obligations to obtain, verify, and record information about the beneficial owners of its legal entity customers;

(j) Legal Action Notice. Prompt written notice of any legal actions, investigations or proceedings pending or threatened in writing against Borrower or any of its Subsidiaries that could reasonably be expected to result in damages or costs to Borrower or any of its Subsidiaries of, individually or in the aggregate, $100,000.00 or more;

(k) Tort Claim Notice. If Borrower shall acquire a commercial tort claim in an aggregate amount of $100,000.00 or more, Borrower shall promptly notify Bank in a writing signed by Borrower of the general details thereof, and grant to Bank in such writing a security interest therein and in the proceeds thereof, all upon the terms of this Agreement, with such writing to be in form and substance reasonably satisfactory to Bank;

(l) Government Filings. Within five (5) days after the same are sent or received, copies of all material and non-routine correspondence, reports, documents, and other filings by Borrower or any of its Subsidiaries with any Governmental Authority regarding compliance with or maintenance of Governmental Approvals or Applicable Law or that could reasonably be expected to have a material effect on any of the Governmental Approvals or otherwise on the business of Borrower or any of its Subsidiaries;

(m) Registered Organization. If Borrower is not a Registered Organization as of the Effective Date but later becomes one, promptly notify Bank of such occurrence and provide Bank with Borrower's organizational identification number;

(n) Default. Prompt written notice of the occurrence of a Default or Event of Default; and

(o) Other Information. Promptly, from time to time, such other information regarding Borrower or any of its Subsidiaries or compliance with the terms of any Loan Documents as reasonably requested by Bank.

Any submission by Borrower of a Compliance Statement or any other financial statement submitted to the Financial Statement Repository pursuant to this Section 5.3 or otherwise submitted to Bank shall be deemed to be a representation by Borrower that (i) as of the date of such Compliance Statement or other financial statement, the information and calculations set forth therein are true and correct, (ii) as of the end of the compliance period set forth in such submission, Borrower is in complete compliance with all required covenants except as noted in such Compliance Statement or other financial statement, as applicable, (iii) as of the date of such submission, no Events of Default have occurred or are continuing, except as noted in such Compliance Statement (iv) all representations and warranties other than any representations or warranties that are made as of a specific date in Section 4 remain true and correct in all material respects as of the date of such submission except as noted in such Compliance Statement or other financial statement, as applicable, (v) as of the date of such submission, Borrower and each of its Subsidiaries has timely filed all required tax returns and reports, and Borrower has timely paid all foreign, federal, state, and local taxes, assessments, deposits and contributions owed by Borrower except as otherwise permitted pursuant to the terms of Section 4.8, and (vi) as of the date of such submission, no Liens have been levied or claims made against Borrower or any of its Subsidiaries relating to unpaid employee payroll or benefits of which Borrower has not previously provided written notification to Bank.

5.4 Taxes; Pensions.

(a) Timely file, and require each of its Subsidiaries to timely file (in each case, unless subject to a valid extension), all required tax returns and reports and timely pay, and require each of its Subsidiaries to timely pay, all foreign, federal, state, and local taxes, assessments, deposits, and contributions owed by Borrower and each of its Subsidiaries, except for deferred payment of any taxes contested pursuant to the terms of Section 4.8(a) hereof, and shall deliver to Bank, on demand, appropriate certificates attesting to such payments, and pay, and require each of its Subsidiaries to pay, all amounts necessary to fund all present pension, profit sharing and deferred compensation plans in accordance with their terms.

(b) To the extent Borrower or any of its Subsidiaries defers payment of any contested taxes, (i) notify Bank in writing of the commencement of, and any material development in, the proceedings, and (ii) post bonds or take any other steps required to prevent the Governmental Authority levying such contested taxes from obtaining a Lien upon any of the Collateral that is other than a "Permitted Lien."

5.5 Access to Collateral; Books and Records. At reasonable times, on one (1) Business Days' notice (provided no notice is required if an Event of Default has occurred and is continuing), Bank, or its agents, shall have the right to inspect the Collateral and the right to audit and copy Borrower's Books. Such inspections and audits shall be conducted no more often than once every 12 months, unless an Event of Default has occurred and is continuing, in which case, such inspections and audits shall occur as often as Bank shall determine is necessary. The foregoing inspections and audits shall be conducted at Borrower's expense and the charge therefor shall be $1,000.00 per person per day (or such higher amount as shall represent Bank's then-current standard charge for the same), plus reasonable and documented out-of-pocket expenses. In the event Borrower and Bank schedule an audit more than eight (8) days in advance, and Borrower cancels or seeks to or reschedules the audit with less than eight (8) days written notice to Bank, then (without limiting any of Bank's rights or remedies) Borrower shall pay Bank a fee of $2,000.00 plus any out-of-pocket expenses incurred by Bank to compensate Bank for the anticipated costs and expenses of the cancellation or rescheduling.

5.6 Insurance.

(a) Keep its business and the Collateral insured for risks and in amounts standard for companies in Borrower's industry and location and as Bank may reasonably request. Insurance policies shall be in a form, with financially sound and reputable insurance companies that are not Affiliates of Borrower, and in amounts that are reasonably satisfactory to Bank.

(b) All property policies shall have a lender's loss payable endorsement showing Bank as lender loss payee. All liability policies shall show, or have endorsements showing, Bank as an additional insured. Bank shall be named as lender loss payee and/or additional insured with respect to any such insurance providing coverage in respect of any Collateral.

(c) Ensure that proceeds payable under any property policy are, at Bank's option, payable to Bank on account of the Obligations. Notwithstanding the foregoing, (a) so long as no Event of Default has occurred and is continuing, Borrower shall have the option of applying the proceeds of any casualty policy up to $300,000.00 individually and in the aggregate, for all losses under all casualty policies in any one year, toward the replacement or repair of destroyed or damaged property; provided that any such replaced or repaired property (i) shall be of equal or like value as the replaced or repaired Collateral, and (ii) shall be deemed Collateral in which Bank has been granted a first priority security interest, and (b) after the occurrence and during the continuance of an Event of Default, all proceeds payable under such casualty policy shall, at the option of Bank, be payable to Bank on the account of the Obligations.

(d) At Bank's request, Borrower shall deliver certified copies of insurance policies and evidence of all premium payments. Each provider of any such insurance required under this Section 5.6 shall agree, by endorsement upon the policy or policies issued by it or by independent instruments furnished to Bank, that it will give Bank thirty (30) days' prior written notice before any such policy or policies shall be canceled or altered in any material respect. If Borrower fails to obtain insurance as required under this Section 5.6 or to pay any amount or furnish any required proof of payment to third persons and Bank, Bank may make all or part of such payment or obtain such insurance policies required in this Section 5.6, and take any action under the policies Bank deems prudent.

5.7 Accounts.

(a) Maintain all of Borrower's, any of its Subsidiaries' (excluding Securities Corp.), and any Guarantor's operating accounts, depository accounts and excess cash with Bank or Bank's Affiliates. In addition to the foregoing, Borrower shall at all times have on deposit in operating and depository accounts maintained in the name of Borrower with Bank, unrestricted and unencumbered cash in an amount equal to the lesser of (i) one hundred percent (100.0%) of the Dollar value of Borrower's consolidated cash, including any Subsidiaries', Affiliates', or related entities' cash, in the aggregate, at all financial institutions, and (ii) one hundred ten percent (110.0%) of the then-outstanding Obligations of Borrower to Bank.

(b) In addition to the foregoing, Borrower, any Subsidiary of Borrower, and any Guarantor shall obtain any business credit card and letter of credit exclusively from Bank (other than the Permitted American Express Credit Cards).

(c) In addition to and without limiting the restrictions in (a), Borrower shall provide Bank five (5) days prior written notice before establishing any Collateral Account at or with any bank or financial institution other than Bank or Bank's Affiliates. For each Collateral Account that Borrower at any time maintains, Borrower shall cause the applicable bank or financial institution (other than Bank) at or with which any Collateral Account is maintained to execute and deliver a Control Agreement or other appropriate instrument with respect to such Collateral Account to perfect Bank's Lien in such Collateral Account in accordance with the terms hereunder which Control Agreement may not be terminated without the prior written consent of Bank. The provisions of the previous sentence shall not apply to deposit accounts exclusively used for payroll, payroll taxes, and other employee wage and benefit payments to or for the benefit of Borrower's employees and identified to Bank by Borrower as such.

5.8 Protection of Intellectual Property Rights.

(a) (i) Use commercially reasonable efforts to protect, defend, and maintain the validity and enforceability of Borrower's and each Subsidiary's Intellectual Property, material to its business, except to the extent that such failure to do so would not reasonably be expected to have a material adverse effect on Borrower's business or operations; (ii) promptly advise Bank in writing of infringements or any other event that could reasonably be expected to materially and adversely affect the value Borrower's and each Subsidiary's Intellectual Property; and (iii) not allow any Intellectual Property material to Borrower's or any Subsidiary's business to be abandoned, forfeited, or dedicated to the public without Bank's written consent.

(b) Provide written notice to Bank within thirty (30) days of entering or becoming bound by any Restricted License (other than over-the-counter software that is commercially available to the public). Borrower shall take such commercially reasonable steps as Bank requests to obtain the consent of, or waiver by, any person whose consent or waiver is necessary for (i) any such Restricted License to be deemed "Collateral" and for Bank to have a security interest in it that might otherwise be restricted or prohibited by law or by the terms of any such Restricted License, whether now existing or entered into in the future, and (ii) Bank to have the ability in the event of a liquidation of any Collateral to dispose of such Collateral in accordance with Bank's rights and remedies under this Agreement and the other Loan Documents.

5.9 Litigation Cooperation. From the date hereof and continuing through the termination of this Agreement, make available to Bank, without expense to Bank, Borrower and its officers, employees, and agents and Borrower's books and records, to the extent that Bank may deem them reasonably necessary to prosecute or defend any third-party suit or proceeding instituted by or against Bank with respect to any Collateral or relating to Borrower (excluding confidential or privileged attorney-client communications).

5.10 Inventory; Returns. Keep all Inventory in good and marketable condition, free from material defects. Returns and allowances between Borrower and its Account Debtors shall follow Borrower's customary practices as they exist at the Effective Date. Borrower shall promptly notify Bank of all returns, recoveries, disputes and claims that involve more than $50,000.00.

5.11 Further Assurances. Execute any further instruments and take such further action as Bank reasonably requests to perfect, protect, ensure the priority of or continue Bank's Lien on the Collateral or to effect the purposes of this Agreement.

5.12 Sanctions. (a) Not, and not permit any of its Subsidiaries to, engage in any of the activities described in Section 4.10 in the future; (b) not, and not permit any of its Subsidiaries to, become a Sanctioned Person; (c) ensure that the proceeds of the Obligations are not used to violate any Sanctions; and (d) deliver to Bank any certification or other evidence requested from time to time by Bank in its sole discretion, confirming each such Person's compliance with this Section 5.12. In addition, have implemented, and will consistently apply while this Agreement is in effect, procedures to ensure that the representations and warranties in Section 4.10 remain true and correct while this Agreement is in effect.

6 NEGATIVE COVENANTS

Borrower shall not do any of the following without Bank's prior written consent:

6.1 Dispositions. Convey, sell, lease, transfer, assign, or otherwise dispose of (including, without limitation, pursuant to a Division) (collectively, "**Transfer**"), or permit any of its Subsidiaries to Transfer, all or any part of its business or property, except for Transfers (a) of Inventory in the ordinary course of business; (b) of worn-out or obsolete, or surplus Equipment that is, in the reasonable judgment of Borrower, no longer economically practicable to maintain or useful in the ordinary course of business of Borrower; (c) consisting of Permitted Liens and Permitted Investments; (d) consisting of the sale or issuance of any stock, partnership, membership, or other ownership interest or other equity securities of Borrower permitted under Section 6.2 of this Agreement; (e) consisting of Borrower's or its Subsidiaries' use or transfer of money or Cash Equivalents in a manner that is not prohibited by the terms of this Agreement or the other Loan Documents; (f) consisting of non-exclusive licenses for the use of the property of Borrower or its Subsidiaries in the ordinary course of business and licenses for the use of property of Borrower or its Subsidiaries that would not result in a legal transfer of title of the licensed property but that may be exclusive in respects other than territory (including as to a particular product candidate or candidates) and that may be exclusive as to territory only as to one or more discrete geographical areas outside of the United States; and (g) other Transfers not otherwise permitted in clauses (a) through (f) above involving tangible assets of Borrower having a fair market value of not more than $100,000.00 in the aggregate (for all such Transfers) in any fiscal year so long as no Event of Default has occurred or would occur immediately following any such Transfer.

6.2 Changes in Business, Management, Control, or Business Locations. (a) Engage in or permit any of its Subsidiaries to engage in any business other than the businesses currently engaged in by Borrower and such Subsidiary, as applicable, or reasonably related thereto; (b) liquidate or dissolve or permit any of its Subsidiaries to liquidate or dissolve; (c) fail to provide notice to Bank of any Key Person departing from or ceasing to be employed by Borrower within ten (10) days after such Key Person's departure from Borrower; (d) permit, allow or suffer to occur any Change in Control; or (e) without at least 30 days' prior written notice to Bank, (i) add any new offices or business locations, including warehouses (unless such new offices or business locations contain less than $100,000.00

in Borrower's assets or property) or deliver any portion of the Collateral valued, individually or in the aggregate, in excess of $100,000.00 to a bailee at a location other than to a bailee and at a location already disclosed in the Perfection Certificate, (ii) change its jurisdiction of organization, (iii) change its organizational structure or type, (iv) change its legal name, or (v) change any organizational number (if any) assigned by its jurisdiction of organization. If Borrower intends to add any new offices or business locations, including warehouses, containing in excess of $100,000.00 of Borrower's assets or property, then Borrower will cause the landlord of any such new offices or business locations, including warehouses, to execute and deliver a landlord consent in form and substance satisfactory to Bank. If Borrower intends to deliver any portion of the Collateral valued, individually or in the aggregate, in excess of $100,000.00 to a bailee, and Bank and such bailee are not already parties to a bailee agreement governing both the Collateral and the location to which Borrower intends to deliver the Collateral, then Borrower will cause such bailee to execute and deliver a bailee agreement in form and substance satisfactory to Bank.

6.3 Mergers or Acquisitions. Merge or consolidate, or permit any of its Subsidiaries to merge or consolidate, with any other Person, or acquire, or permit any of its Subsidiaries to acquire, all or substantially all of the stock, partnership, membership, or other ownership interest or other equity securities or property of another Person (including, without limitation, by the formation of any Subsidiary or pursuant to a Division). A Subsidiary may merge or consolidate into another Subsidiary or into Borrower.

6.4 Indebtedness. Create, incur, assume, or be liable for any Indebtedness, or permit any Subsidiary to do so, other than Permitted Indebtedness.

6.5 Encumbrance. Create, incur, allow, or suffer to exist any Lien on any of its property, or assign or convey any right to receive income, including the sale of any Accounts, or permit any of its Subsidiaries to do so, except for Permitted Liens, permit any Collateral not to be subject to the first priority security interest granted herein, except for Permitted Liens, or enter into any agreement, document, instrument, or other arrangement (except with or in favor of Bank) with any Person which directly or indirectly prohibits or has the effect of prohibiting Borrower or any Subsidiary from assigning, mortgaging, pledging, granting a security interest in or upon, or encumbering any of Borrower's or any Subsidiary's Intellectual Property, except (i) as otherwise permitted in Section 6.1 hereof and the definition of "Permitted Liens" herein, or (ii) for customary restrictions on assignment, transfer and encumbrances in license agreements under which Borrower or any Subsidiary is the licensee.

6.6 Maintenance of Collateral Accounts. Maintain any Collateral Account except pursuant to the terms of Section 5.7(c).

6.7 Distributions; Investments. (a) Pay any dividends or make any distribution or payment or redeem, retire or purchase any stock, partnership, membership, or other ownership interest or other equity securities; or (b) directly or indirectly make any Investment (including, without limitation, by the formation of any Subsidiary) other than Permitted Investments, or permit any of its Subsidiaries to do so; provided that Borrower may (i) convert any of its convertible securities into other securities pursuant to the terms of such convertible securities or otherwise in exchange thereof, (ii) pay dividends solely in common stock; and (iii) repurchase the stock of former employees or consultants pursuant to stock repurchase agreements so long as an Event of Default does not exist at the time of any such repurchase and would not exist after giving effect to any such repurchase, provided that the aggregate amount of all such repurchases does not exceed $100,000.00 per fiscal year.

Notwithstanding the foregoing, and for the avoidance of doubt, this Section 6.7 shall not prohibit (i) Borrower from granting equity awards to its employees, directors, consultants or advisors through Borrower's equity incentive plan or as inducement grants in accordance with Nasdaq Listing Rule 5636(c)(4); or (ii) the withholding of shares of common stock upon the vesting of performance stock units and restricted stock units issued under Borrower's equity incentive plan upon vesting of such stock units.

6.8 Transactions with Affiliates. Directly or indirectly enter into or permit to exist any material transaction with any Affiliate of Borrower, except for (a) transactions that are in the ordinary course of Borrower's business, upon fair and reasonable terms that are no less favorable to Borrower than would be obtained in an arm's-length transaction with a non-affiliated Person and (b) transactions of the type described in and permitted under Section 6.7 of this Agreement.

6.9 Subordinated Debt. Except as expressly permitted under the terms of the subordination, intercreditor, or other similar agreement to which any Subordinated Debt is subject: (a) make or permit any payment on such Subordinated Debt; or (b) amend any provision in any document relating to such Subordinated Debt which would increase the amount thereof, provide for earlier or greater principal, interest, or other payments thereon, or adversely affect the subordination thereof to Obligations owed to Bank.

6.10 Compliance. (a) Become an "investment company" or a company controlled by an "investment company", under the Investment Company Act of 1940, as amended, or undertake as one of its important activities extending credit to purchase or carry margin stock (as defined in Regulation U of the Board of Governors of the Federal Reserve System), or use the proceeds of any Credit Extension for that purpose; (b)(i) fail to meet the minimum funding requirements of ERISA, (ii) permit a Reportable Event or Prohibited Transaction, as defined in ERISA, to occur, (iii) fail to comply with the Federal Fair Labor Standards Act, or (iv) violate any other law or regulation, if the foregoing subclauses (i) through (iv), individually or in the aggregate, could reasonably be expected to have a material adverse effect on Borrower's business or operations, or permit any of its Subsidiaries to do so; or (c) withdraw or permit any Subsidiary to withdraw from participation in, permit partial or complete termination of, or permit the occurrence of any other event with respect to, any present pension, profit sharing, and deferred compensation plan which could reasonably be expected to result in any liability of Borrower, including any liability to the Pension Benefit Guaranty Corporation or its successors or any other Governmental Authority.

7 EVENTS OF DEFAULT

Any one of the following shall constitute an event of default (an "**Event of Default**") under this Agreement:

7.1 Payment Default. Borrower fails to (a) make any payment of principal or interest on any Credit Extension on its due date, or (b) pay any other Obligations within three (3) Business Days after such Obligations are due and payable (which three (3) Business Day cure period shall not apply to payments due on the Term Loan Maturity Date). During the cure period, the failure to make or pay any payment specified under clause (b) hereunder is not an Event of Default (but no Credit Extension will be made during the cure period);

7.2 Covenant Default.

(a) Borrower fails or neglects to perform any obligation in Section 5 (other than Sections 5.2 (Government Compliance), 5.9 (Litigation Cooperation), 5.10 (Inventory; Returns) and 5.11 (Further Assurances)) or violates any covenant in Section 6; or

(b) Borrower fails or neglects to perform, keep, or observe any other term, provision, condition, covenant, or agreement contained in this Agreement or any Loan Documents, and as to any default (other than those specified in this Section 7) under such other term, provision, condition, covenant, or agreement that can be cured, has failed to cure the default within ten (10) days after the occurrence thereof; provided, however, that if the default cannot by its nature be cured within the ten (10)-day period or cannot after diligent attempts by Borrower be cured within such ten (10) day period, and such default is likely to be cured within a reasonable time, then Borrower shall have an additional period (which shall not in any case exceed 30 days) to attempt to cure such default, and within such reasonable time period the failure to cure the default shall not be deemed an Event of Default (but no Credit Extensions shall be made during such cure period). Cure periods provided under this section shall not apply, among other things, to financial covenants or any other covenants that are required to be satisfied, completed, or tested by a date certain or any covenants set forth in clause (a) above;

7.3 Material Adverse Change. A Material Adverse Change occurs;

7.4 Attachment; Levy; Restraint on Business.

(a) (i) The service of process seeking to attach, by trustee or similar process, any funds of Borrower or any Subsidiary, or (ii) a notice of lien or levy is filed against any of Borrower's or any of its Subsidiaries' assets by any Governmental Authority, and the same under subclauses (i) and (ii) hereof are not, within ten (10) days after the occurrence thereof, discharged or stayed (whether through the posting of a bond or otherwise); provided, however, no Credit Extensions shall be made during any ten (10) day cure period; or

(b) (i) any material portion of Borrower's or any of its Subsidiaries' assets is attached, seized, levied on, or comes into possession of a trustee or receiver, or (ii) any court order enjoins, restrains, or prevents Borrower or any of its Subsidiaries from conducting all or any material part of its business;

7.5 Insolvency. (a) Borrower or any of its Subsidiaries are unable to pay its debts (including trade debts) as they become due or otherwise becomes insolvent; (b) Borrower or any of its Subsidiaries begins an Insolvency Proceeding; or (c) an Insolvency Proceeding is begun against Borrower or any of its Subsidiaries and is not dismissed or stayed within 45 days (but no Credit Extensions shall be made while any of the conditions described in clause (a) exist or until any Insolvency Proceeding is dismissed);

7.6 Other Agreements. There is, under any agreement to which Borrower, any of Borrower's Subsidiaries, or any Guarantor is a party with a third party or parties, (a) any default resulting in a right by such third party or parties, whether or not exercised, to accelerate the maturity of any Indebtedness in an amount individually or in the aggregate in excess of $100,000.00; or (b) any breach or default by Borrower, any of Borrower's Subsidiaries, or any Guarantor, the result of which could have a material adverse effect on Borrower's, any of Borrower's Subsidiaries', or any Guarantor's business or operations;

7.7 Judgments; Penalties. One or more fines, penalties or final judgments, orders or decrees for the payment of money in an amount, individually or in the aggregate, of at least $100,000.00 (not covered by independent third-party insurance as to which liability has been accepted by such insurance carrier) shall be rendered against Borrower or any of its Subsidiaries by any Governmental Authority, and the same are not, within ten (10) days after the entry, assessment or issuance thereof, discharged, or after execution thereof, or stayed pending appeal, or such judgments are not discharged prior to the expiration of any such stay (provided that no Credit Extensions will be made prior to the discharge, or stay of such fine, penalty, judgment, order or decree);

7.8 Misrepresentations. Borrower or any of its Subsidiaries or any Person acting for Borrower or any of its Subsidiaries makes any representation, warranty, or other statement now or later in this Agreement, any Loan Document or in any writing delivered to Bank or to induce Bank to enter this Agreement or any Loan Document, and such representation, warranty, or other statement is incorrect in any material respect when made (it being agreed and acknowledged by Bank that the projections and forecasts provided by Borrower or any of its Subsidiaries in good faith and based upon reasonable assumptions are not viewed as facts and that actual results during the period or periods covered by such projections and forecasts may differ from the projected or forecasted results);

7.9 Subordinated Debt. If: (a) any document, instrument, or agreement evidencing any Subordinated Debt shall for any reason be revoked or invalidated or otherwise cease to be in full force and effect (other than in accordance with its terms), or any Person (other than Bank) shall be in breach thereof or contest in any manner the validity or enforceability thereof or deny that it has any further liability or obligation thereunder; (b) a default or event of default (however defined) has occurred under any document, instrument, or agreement evidencing any Subordinated Debt, which default shall not have been cured or waived within any applicable grace period; or (c) the Obligations shall for any reason be subordinated or shall not have the priority contemplated by this Agreement or any applicable subordination or intercreditor agreement between any holder of the Subordinated Debt and the Bank;

7.10 Lien Priority. There is a material impairment in the perfection or priority of Bank's security interest in the Collateral;

7.11 Guaranty. (a) Any guaranty of any Obligations terminates or ceases for any reason to be in full force and effect; (b) any Guarantor does not perform any obligation or covenant under any guaranty of the Obligations; (c) any circumstance described in Sections 7.3, 7.4, 7.5, 7.6, 7.7, or 7.8 of this Agreement occurs with respect to any Guarantor, (d) the death, liquidation, winding up, or termination of existence of any Guarantor; or (e) (i) a material impairment in the perfection or priority of Bank's Lien in the collateral provided by Guarantor or in the value of such collateral, or (ii) a material adverse change in the general affairs, management, results of operation, condition (financial or otherwise), or the prospect of repayment of the Obligations occurs with respect to any Guarantor; or

7.12 Governmental Approvals. Any Governmental Approval shall have been (a) revoked, rescinded, suspended, modified in an adverse manner or not renewed in the ordinary course for a full term or (b) subject to any decision by a Governmental Authority that designates a hearing with respect to any applications for renewal of any of such Governmental Approval or that could result in the Governmental Authority taking any of the actions described in clause (a) above, and such decision or such revocation, rescission, suspension, modification or non-renewal (i) causes or could reasonably be expected to cause a Material Adverse Change, or (ii) adversely affects the legal qualifications of Borrower or any of its Subsidiaries to hold such Governmental Approval in any applicable jurisdiction and such revocation, rescission, suspension, modification or non-renewal could reasonably be expected to affect the status of or legal qualifications of Borrower or any of its Subsidiaries to hold any Governmental Approval in any other jurisdiction.

7.13 Delisting. Borrower's shares are delisted from the applicable exchange or market because of Borrower's failure to comply with continued listing standards thereof or due to a voluntary delisting which results in such shares not being listed on such exchange or market.

8 BANK'S RIGHTS AND REMEDIES

8.1 Rights and Remedies. Upon the occurrence and during the continuance of an Event of Default, Bank may, without notice or demand, do any or all of the following:

(a) declare all Obligations immediately due and payable (but if an Event of Default described in Section 7.5 occurs, all Obligations are immediately due and payable without any action by Bank);

(b) stop advancing money or extending credit for Borrower's benefit under this Agreement or under any other agreement between Borrower and Bank;

(c) demand that Borrower (i) deposit cash with Bank in an amount equal to at least (A) 105.0% of the aggregate face amount of any Letters of Credit denominated in Dollars remaining undrawn, and (B) 110.0% of the Dollar Equivalent of the aggregate face amount of any Letters of Credit denominated in a Foreign Currency remaining undrawn (plus, in each case, all interest, fees, and costs due or estimated by Bank in its commercially reasonable judgment to become due in connection therewith), to secure all of the Obligations relating to such Letters of Credit, as collateral security for the repayment of any future drawings under such Letters of Credit, and Borrower shall forthwith deposit and pay such amounts, and (ii) pay in advance all letter of credit fees scheduled to be paid or payable over the remaining term of any Letters of Credit;

(d) terminate any FX Contracts (it being understood and agreed that (i) Bank is not obligated to deliver the currency which Borrower has contracted to receive under any FX Contract, and Bank may cover its exposure for any FX Contracts by purchasing or selling currency in the interbank market as Bank deems appropriate; (ii) Borrower shall be liable for all losses, damages, costs, margin obligations, and expenses incurred by Bank arising from Borrower's failure to satisfy its obligations under any FX Contract or the execution of any FX Contract; and (iii) Bank shall not be liable to Borrower for any gain in value of a FX Contract that Bank may obtain in covering Borrower's breach);

(e) verify the amount of, demand payment of and performance under, and collect any Accounts and General Intangibles, settle or adjust disputes and claims directly with Account Debtors for amounts on terms and in any order that Bank considers advisable, and notify any Person owing Borrower money of Bank's security interest in such funds;

(f) make any payments and do any acts it considers necessary or reasonable to protect the Collateral and/or its security interest in the Collateral. Borrower shall assemble the Collateral if Bank requests and make it available as Bank designates. Bank may enter premises where the Collateral is located, take and maintain possession of any part of the Collateral, and pay, purchase, contest, or compromise any Lien which appears to be prior or superior to its security interest and pay all expenses incurred. Borrower grants Bank a license to enter and occupy any of its premises, without charge, to exercise any of Bank's rights or remedies;

(g) apply to the Obligations any (i) balances and deposits of Borrower it holds, or (ii) amount held by Bank owing to or for the credit or the account of Borrower;

(h) ship, reclaim, recover, store, finish, maintain, repair, prepare for sale, advertise for sale, and sell the Collateral. For use solely upon the occurrence and during the continuation of an Event of Default, Bank is hereby granted a non-exclusive, royalty-free license or other right to use, without charge, Borrower's labels, Patents, Copyrights, mask works, rights of use of any name, trade secrets, trade names, Trademarks, and advertising matter, or any similar property as it pertains to the Collateral, in completing production of, advertising for sale, and selling any Collateral and, in connection with Bank's exercise of its rights under this Section 8.1, Borrower's rights under all licenses and all franchise agreements inure to Bank's benefit;

(i) place a "hold" on any account maintained with Bank and/or deliver a notice of exclusive control, any entitlement order, or other directions or instructions pursuant to any Control Agreement or similar agreements providing control of any Collateral;

(j) demand and receive possession of Borrower's Books; and

(k) exercise all rights and remedies available to Bank under the Loan Documents or at law or equity, including all remedies provided under the Code or any Applicable Law (including disposal of the Collateral pursuant to the terms thereof).

8.2 Power of Attorney. Borrower hereby irrevocably appoints Bank as its true and lawful attorney-in-fact, (a) exercisable upon the occurrence and during the continuance of an Event of Default, to: (i) endorse Borrower's name on any checks, payment instruments, or other forms of payment or security; (ii) sign Borrower's name on any invoice or bill of lading for any Account or drafts against Account Debtors; (iii) demand, collect, sue, and give releases to any Account Debtor for monies due, settle and adjust disputes and claims about the Accounts directly with Account Debtors, and compromise, prosecute, or defend any action, claim, case, or proceeding about any Collateral (including filing a claim or voting a claim in any bankruptcy case in Bank's or Borrower's name, as Bank chooses); (iv) make, settle, and adjust all claims under Borrower's insurance policies; (v) pay, contest, or settle any Lien, charge, encumbrance, security interest, or other claim in or to the Collateral, or any judgment based thereon, or otherwise take any action to terminate or discharge the same; and (vi) transfer the Collateral into the name of Bank or a third party as the Code permits; and (b) regardless of whether an Event of Default has occurred, to sign Borrower's name on any documents necessary to perfect or continue the perfection of Bank's security interest in the Collateral. Bank's foregoing appointment as Borrower's attorney in fact, and all of Bank's rights and powers, coupled with an interest, are irrevocable until such time as all Obligations (other than inchoate indemnity obligations, any obligations, which by their terms are to survive termination of this Agreement and any Obligations under Bank Service Agreements that are cash collateralized in accordance with Section 3.3) have been satisfied in full, Bank is under no further obligation to make Credit Extensions and the Loan Documents have been terminated. Bank shall not incur any liability in connection with or arising from the exercise of such power of attorney and shall have no obligation to exercise any of the foregoing rights and remedies.

8.3 Protective Payments. If Borrower fails to obtain the insurance called for by Section 5.5 or fails to pay any premium thereon or fails to pay any other amount which Borrower is obligated to pay under this Agreement or any other Loan Document or which may be required to preserve the Collateral, Bank may obtain such insurance or make such payment, and all amounts so paid by Bank are Bank Expenses and immediately due and payable, bearing interest at the then highest rate applicable to the Obligations, and secured by the Collateral. Bank will make reasonable efforts to provide Borrower with notice of Bank obtaining such insurance at the time it is obtained or within a reasonable time thereafter. No payments by Bank under this Section 8.3 are deemed an agreement to make similar payments in the future or Bank's waiver of any Event of Default.

8.4 Application of Payments and Proceeds. If an Event of Default has occurred and is continuing, Bank may apply any funds in its possession, whether from Borrower account balances, payments, proceeds realized as the result of any collection of Accounts or other disposition of the Collateral, or otherwise, to the Obligations in such order as Bank shall determine in its sole discretion. Any surplus shall be paid to Borrower or other Persons legally entitled thereto; Borrower shall remain liable to Bank for any deficiency. If Bank, in its commercially reasonable discretion, directly or indirectly, enters into a deferred payment or other credit transaction with any purchaser at any sale of Collateral, Bank shall have the option, exercisable at any time, of either reducing the Obligations by the principal amount of the purchase price or deferring the reduction of the Obligations until the actual receipt by Bank of cash therefor.

8.5 Bank's Liability for Collateral. Bank's sole duty with respect to the custody, safekeeping, and physical preservation of the Collateral in its possession or under its control, under Section 9-207 of the Code or otherwise, shall be to deal with it in the same manner as Bank deals with its own property consisting of similar instruments or interests. Borrower bears all risk of loss, damage, or destruction of the Collateral.

8.6 No Waiver; Remedies Cumulative. Bank's failure, at any time or times, to require strict performance by Borrower of any provision of this Agreement or any other Loan Document shall not waive, affect, or diminish any right of Bank thereafter to demand strict performance and compliance herewith or therewith. No waiver hereunder shall be effective unless signed by the party granting the waiver and then is only effective for the specific instance and purpose for which it is given. Bank's rights and remedies under this Agreement and the other Loan Documents are cumulative. Bank has all rights and remedies provided under the Code, by law, or in equity. Bank's exercise of one right or remedy is not an election and shall not preclude Bank from exercising any other remedy under this Agreement or other remedy available at law or in equity, and Bank's waiver of any Event of Default is not a continuing waiver. Bank's delay in exercising any remedy is not a waiver, election, or acquiescence.

8.7 Demand Waiver. Except as otherwise expressly set forth herein or in the other Loan Documents, Borrower waives demand, notice of default or dishonor, notice of payment and nonpayment, notice of any default, nonpayment at maturity, release, compromise, settlement, extension, or renewal of accounts, documents, instruments, chattel paper, and guarantees held by Bank on which Borrower is liable.

9 NOTICES

All notices, consents, requests, approvals, demands, or other communication by any party to this Agreement or any other Loan Document must be in writing and shall be deemed to have been validly served, given, or delivered: (a) upon the earlier of actual receipt and three (3) Business Days after deposit in the U.S. mail, first class, registered or certified mail return receipt requested, with proper postage prepaid; (b) upon transmission, when sent by electronic mail; (c) one (1) Business Day after deposit with a reputable overnight courier with all charges prepaid; or (d) when delivered, if hand-delivered by messenger, all of which shall be addressed to the party to be notified and sent to the address or email address indicated below; provided that, for clause (b), if such notice, consent, request, approval, demand, or other communication is not sent during the normal business hours of the recipient, it shall be deemed to have been sent at the opening of business on the next Business Day of the recipient. Bank or Borrower may change its mailing or electronic mail address by giving the other party written notice thereof in accordance with the terms of this Section 9.

If to Borrower:	Cue Biopharma, Inc. 21 Erie Street Cambridge, Massachusetts 02139 Attn: Kerri-Ann Millar Email: kmillar@cuebio.com
with a copy to (which shall not constitute notice):	WilmerHale 60 State Street Boston, Massachusetts 02109 Attn: George W. Shuster, Jr., Esquire & Cynthia Mazareas, Esquire Email: george.shuster@wilmerhale.com cynthia.mazareas@wilmerhale.com

If to Bank: Silicon Valley Bank
275 Grove Street, Suite 2-200
Newton, MA 02466
Attn: Clark Hayes
Email: CHayes@svb.com

with a copy to (which shall not constitute notice): Morrison & Foerster LLP
200 Clarendon Street, Floor 20
Boston, Massachusetts 02116
Attn: David A. Ephraim, Esquire
Email: DEphraim@mofo.com

10 CHOICE OF LAW, VENUE AND JURY TRIAL WAIVER

Except as otherwise expressly provided in any of the Loan Documents, Massachusetts law governs the Loan Documents without regard to principles of conflicts of law that would require the application of the laws of another jurisdiction. Borrower and Bank each irrevocably and unconditionally submit to the exclusive jurisdiction of the State and Federal courts in Boston, Massachusetts; provided, however, that nothing in this Agreement shall be deemed to operate to preclude Bank from bringing suit or taking other legal action in any other jurisdiction with respect to the Loan Documents or to realize on the Collateral or any other security for the Obligations, or to enforce a judgment or other court order in favor of Bank. Borrower expressly, irrevocably and unconditionally submits and consents in advance to such jurisdiction in any action or suit commenced in any such court, and Borrower hereby irrevocably and unconditionally waives, to the fullest extent permitted by Applicable Law, any objection that it may have based upon lack of personal jurisdiction, improper venue, or forum non conveniens and hereby irrevocably and unconditionally consents to the granting of such legal or equitable relief as is deemed appropriate by such court. Borrower hereby waives personal service of the summons, complaints, and other process issued in such action or suit and agrees that service of such summons, complaints, and other process may be made by registered or certified mail addressed to Borrower at the address set forth in, or subsequently provided by Borrower in accordance with, Section 9 of this Agreement and that service so made shall be deemed completed upon the earlier to occur of Borrower's actual receipt thereof or three (3) days after deposit in the U.S. mails, proper postage prepaid.

TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, BORROWER AND BANK EACH WAIVES ITS RIGHT TO A JURY TRIAL OF ANY CLAIM OR CAUSE OF ACTION ARISING OUT OF OR BASED UPON THIS AGREEMENT, THE LOAN DOCUMENTS OR ANY CONTEMPLATED TRANSACTION, INCLUDING CONTRACT, TORT, BREACH OF DUTY AND ALL OTHER CLAIMS. THIS WAIVER IS A MATERIAL INDUCEMENT FOR THE PARTIES HERETO TO ENTER INTO THIS AGREEMENT. EACH PARTY HERETO HAS REVIEWED THIS WAIVER WITH ITS COUNSEL.

This Section 10 shall survive the termination of this Agreement and the repayment of all Obligations.

11 GENERAL PROVISIONS

11.1 Termination Prior to Maturity Date; Survival. All covenants, representations and warranties made in this Agreement shall continue in full force until this Agreement has terminated pursuant to its terms and all Obligations (other than inchoate indemnity obligations) have been satisfied. So long as Borrower has satisfied the Obligations (other than inchoate indemnity obligations, and any other obligations which, by their terms, are to survive the termination of this Agreement and the repayment of all Obligations, and any Obligations under Bank Services Agreements that are cash collateralized in accordance with Section 3.3 of this Agreement), this Agreement may be terminated prior to the Term Loan Maturity Date by Borrower, effective three (3) Business Days after written notice of termination is given to Bank. Those obligations that are expressly specified in this Agreement as surviving this Agreement's termination and the repayment of all Obligations shall continue to survive notwithstanding this Agreement's termination and the repayment of all Obligations.

11.2 Successors and Assigns. This Agreement binds and is for the benefit of the successors and permitted assigns of each party. Borrower may not assign or transfer this Agreement or any rights or obligations under it without Bank's prior written consent (which may be granted or withheld in Bank's sole discretion) and any other attempted assignment or transfer by Borrower shall be null and void. Bank has the right, without the consent of or notice to Borrower, to sell, transfer, assign, negotiate, or grant participation in all or any part of, or any interest in, Bank's obligations, rights, and benefits under this Agreement and the other Loan Documents. Notwithstanding the foregoing, so long as no Event of Default shall have occurred and is continuing, Bank shall not assign its interest in the Loan Documents to any Person who in the reasonable estimation of Bank is (a) a direct competitor of Borrower, whether as an operating company or direct or indirect parent with voting control over such operating company, or (b) a vulture fund or distressed debt fund.

11.3 Indemnification.

(a) General Indemnification. Borrower shall indemnify, defend, and hold Bank and its Affiliates and the partners, directors, officers, employees, agents, trustees, administrators, managers, advisors, and representatives of Bank and its Affiliates (each, an "**Indemnified Person**") harmless against: all losses, claims, damages, liabilities, and related reasonable and documented out-of-pocket expenses (including Bank Expenses and the reasonable and documented out-of-pocket fees, charges, and disbursements of any counsel for any Indemnified Person) (collectively, "**Claims**") arising out of, in connection with, or as a result of (i) the execution or delivery of this Agreement, any other Loan Document, or any agreement or instrument contemplated hereby or thereby, the performance by the parties hereto of their respective obligations hereunder or thereunder, or the consummation of the transactions contemplated hereby or thereby, (ii) any Credit Extension or the use or proposed use of the proceeds therefrom, (iii) any actual or alleged presence or release of hazardous materials on or from any property owned or operated by Borrower or any of its Subsidiaries, or any environmental liability related in any way to Borrower or any of its Subsidiaries, or (iv) any actual or prospective claim, litigation, investigation or proceeding relating to any of the foregoing, whether based on contract, tort, or any other theory, whether brought by a third party or by Borrower, and regardless of whether any Indemnified Person is a party thereto; provided that such indemnity shall not, as to any Indemnified Person, be available to the extent that such losses, claims, damages, liabilities, or related expenses are determined by a court of competent jurisdiction by final and non-appealable judgment to have resulted from the gross negligence or willful misconduct of such Indemnified Person. All amounts due under this Section 11.3 shall be payable promptly after demand therefor. This Section 11.3(a) shall not apply with respect to Taxes, other than any Taxes that represent losses, claims, damages, etc. arising from any non-Tax claim.

(b) Waiver of Consequential Damages, Etc. To the fullest extent permitted by Applicable Law, Borrower shall not assert, and hereby waives, any claim against any Indemnified Person, on any theory of liability, for special, indirect, consequential, or punitive damages (as opposed to direct or actual damages) or any loss of profits arising out of, in connection with, or as a result of, this Agreement, any other Loan Document or any agreement or instrument contemplated hereby, the transactions contemplated hereby or thereby, any Credit Extension, or the use of the proceeds thereof. No Indemnified Person shall be liable for any damages arising from the use by unintended recipients of any information or other materials distributed by it through telecommunications, electronic, or other information transmission systems in connection with this Agreement or the other Loan Documents or the transactions contemplated hereby or thereby.

This Section 11.3 shall survive the termination of this Agreement and the repayment of all Obligations until all statutes of limitation with respect to the Claims, losses, and expenses for which indemnity is given shall have run.

11.4 Time of Essence. Time is of the essence for the performance of all Obligations in this Agreement.

11.5 Severability of Provisions. Each provision of this Agreement is severable from every other provision in determining the enforceability of any provision.

11.6 Amendments in Writing; Waiver; Integration. No purported amendment or modification of any Loan Document, or waiver, discharge, or termination of any obligation under any Loan Document, shall be effective unless, and only to the extent, expressly set forth in a writing signed by each party hereto. Without limiting the generality of the foregoing, no oral promise or statement, nor any action, inaction, delay, failure to require performance, or course of conduct shall operate as, or evidence, an amendment, supplement or waiver or have any other effect on any Loan Document. Any waiver granted shall be limited to the specific circumstance expressly described in it, and shall not apply to any subsequent or other circumstance, whether similar or dissimilar, or give rise to, or evidence, any obligation or commitment to grant any further waiver. The Loan Documents represent the entire agreement about this subject matter and supersede prior negotiations or agreements. All prior agreements, understandings, representations, warranties, and negotiations between the parties about the subject matter of the Loan Documents merge into the Loan Documents.

11.7 Counterparts. This Agreement may be executed in any number of counterparts and by different parties on separate counterparts, each of which, when executed and delivered, is an original, and all taken together, constitute one Agreement. Delivery of an executed signature page of this Agreement by electronic mail transmission shall be effective as delivery of a manually executed counterpart hereof.

11.8 Confidentiality. Bank agrees to maintain the confidentiality of Information (as defined below), except that Information may be disclosed (a) to Bank's Subsidiaries and Affiliates and their respective employees, directors, agents, attorneys, accountants, and other professional advisors (collectively, "**Representatives**" and, together with Bank, collectively, "**Bank Entities**"); (b) to prospective transferees, assignees, credit providers or purchasers of Bank's interests under or in connection with this Agreement and their Representatives (provided, however, any such prospective transferee's, assignee's, credit provider's, purchaser's, or their Representatives shall have entered into an agreement containing provisions substantially the same as those in this Section); (c) as required by law, regulation, subpoena, or other order; (d) to Bank's regulators or as otherwise required or requested in connection with Bank's examination or audit; (e) in connection with the exercise of remedies under the Loan Documents or any action or proceeding relating to this Agreement or any other Loan Document or the enforcement of rights hereunder or thereunder; and (f) to third-party service providers of Bank so long as such service providers have executed a confidentiality agreement with Bank with terms no less restrictive than those contained herein. "**Information**" means all information received from Borrower regarding Borrower or its business, in each case other than information that is either: (i) in the public domain or in Bank's possession when disclosed to Bank, or becomes part of the public domain (other than as a result of its disclosure by Bank in violation of this Agreement) after disclosure to Bank; or (ii) disclosed to Bank by a third party, if Bank does not know that the third party is prohibited from disclosing the information.

11.9 Electronic Execution of Documents. The words "execution," "signed," "signature," and words of like import in any Loan Document shall be deemed to include electronic signatures, including any Electronic Signature as defined in the Electronic Transactions Law (2003 Revision) of the Cayman Islands (the "**Cayman Islands Electronic Signature Law**"), if applicable, or the keeping of records in electronic form, including any Electronic Record, as defined in Cayman Islands Electronic Signature Law, each of which shall be of the same legal effect, validity and enforceability as a manually executed signature or the use of a paper-based recordkeeping systems, as the case may be, to the extent and as provided for in any Applicable Law, including, without limitation, any state law based on the Uniform Electronic Transactions Act or the Cayman Islands Electronic Signature Law; provided, however that sections 8 and 19(3) of the Cayman Islands Electronic Signature Law shall not apply to this Agreement or the execution or delivery thereof.

11.10 Right of Setoff. Borrower hereby grants to Bank a Lien and a right of setoff as security for all Obligations to Bank, whether now existing or hereafter arising upon and against all deposits, credits, collateral and property, now or hereafter in the possession, custody, safekeeping or control of Bank or any entity under the control of Bank (including a subsidiary of Bank) or in transit to any of them, and other obligations owing to Bank or any such entity. At any time after the occurrence and during the continuance of an Event of Default, without demand or notice, Bank may setoff the same or any part thereof and apply the same to any liability or Obligation of Borrower even though unmatured and regardless of the adequacy of any other collateral securing the Obligations. ANY AND ALL RIGHTS TO REQUIRE BANK TO EXERCISE ITS RIGHTS OR REMEDIES WITH RESPECT TO ANY OTHER COLLATERAL WHICH SECURES THE OBLIGATIONS, PRIOR TO EXERCISING ITS RIGHT OF SETOFF WITH RESPECT TO SUCH DEPOSITS, CREDITS OR OTHER PROPERTY OF BORROWER, ARE HEREBY KNOWINGLY, VOLUNTARILY, AND IRREVOCABLY WAIVED.

11.11 Captions and Section References. The headings used in this Agreement are for convenience only and shall not affect the interpretation of this Agreement. Unless indicated otherwise, section references herein are to sections of this Agreement.

11.12 Construction of Agreement. The parties hereto mutually acknowledge that they and their attorneys have participated in the preparation and negotiation of this Agreement. In cases of uncertainty this Agreement shall be construed without regard to which of the parties caused the uncertainty to exist.

11.13 Relationship. The relationship of the parties to this Agreement is determined solely by the provisions of this Agreement. The parties do not intend to create any agency, partnership, joint venture, trust, fiduciary, or other relationship with duties or incidents different from those of parties to an arm's-length contract.

11.14 Third Parties. Nothing in this Agreement, whether express or implied, is intended to: (a) confer any benefits, rights, or remedies under or by reason of this Agreement on any Persons other than the express parties to it and their respective permitted successors and assigns; (b) relieve or discharge the obligation or liability of any Person not an express party to this Agreement; or (c) give any Person not an express party to this Agreement any right of subrogation or action against any party to this Agreement.

11.15 Anti-Terrorism Law. Bank hereby notifies Borrower that, pursuant to the requirements of Anti-Terrorism Law, Bank may be required to obtain, verify, and record information that identifies Borrower, which information may include the name and address of Borrower and other information that will allow Bank to identify Borrower in accordance with Anti-Terrorism Law. Borrower hereby agrees to take any action necessary to enable Bank to comply with the requirements of Anti-Terrorism Law.

12 ACCOUNTING TERMS AND OTHER DEFINITIONS

12.1 Accounting and Other Terms.

(a) Accounting terms not defined in this Agreement shall be construed following GAAP. Calculations and determinations must be made following GAAP (except for with respect to unaudited financial statements for the absence of footnotes and subject to year-end audit adjustments), provided that if at any time any change in GAAP would affect the computation of any financial ratio or requirement set forth in any Loan Document, and either Borrower or Bank shall so request, Borrower and Bank shall negotiate in good faith to amend such ratio or requirement to preserve the original intent thereof in light of such change in GAAP; provided, further, that, until so amended, (i) such ratio or requirement shall continue to be computed in accordance with GAAP prior to such change therein and (ii) Borrower shall provide Bank financial statements and other documents required under this Agreement or as reasonably requested hereunder setting forth a reconciliation between calculations of such ratio or requirement made before and after giving effect to such change in GAAP. Notwithstanding the foregoing, any obligations of a Person that are or would have been treated as operating leases for purposes of GAAP prior to the issuance by the Financial Accounting Standards Board on February 25, 2016 of an Accounting Standards Update (the "**ASU**") shall continue to be accounted for as operating leases for purposes of all financial definitions, calculations and covenants for purpose of this Agreement (whether or not such operating lease obligations were in effect on such date) notwithstanding the fact that such obligations are required in accordance with the ASU (on a prospective or retroactive basis or otherwise) to be treated as capitalized lease obligations in accordance with GAAP (for the avoidance of doubt, other than for purposes of the delivery of financial statements prepared in accordance with GAAP).

(b) As used in the Loan Documents: (i) the words "shall" or "will" are mandatory, the word "may" is permissive, the word "or" is not exclusive, the words "includes" and "including" are not limiting, the singular includes the plural, and numbers denoting amounts that are set off in brackets are negative; (ii) the term "continuing" in the context of an Event of Default means that the Event of Default has not been remedied (if capable of being remedied) or waived; and (iii) whenever a representation or warranty is made to Borrower's knowledge or awareness, to the "best of" Borrower's knowledge, or with a similar qualification, knowledge or awareness means the actual knowledge, after reasonable investigation, of any Responsible Officer.

12.2 Definitions. Capitalized terms not otherwise defined in this Agreement shall have the meanings set forth in this Section 12.2. All other terms contained in this Agreement, unless otherwise indicated, shall have the meaning provided by the Code to the extent such terms are defined therein. As used in this Agreement, the following capitalized terms have the following meanings:

"**Account**" is, as to any Person, any "account" of such Person as "account" is defined in the Code with such additions to such term as may hereafter be made, and includes, without limitation, all accounts receivable and other sums owing to such Person.

"**Account Debtor**" is any "account debtor" as defined in the Code, with such additions to such term as may hereafter be made.

"**Affiliate**" is, with respect to any Person, each other Person that owns or controls directly or indirectly the Person, any Person that controls or is controlled by or is under common control with the Person, and each of that Person's senior executive officers, directors, partners, and, for any Person that is a limited liability company, that Person's managers and members.

"**Agreement**" is defined in the preamble hereof.

"**Anti-Terrorism Law**" means any law relating to terrorism or money-laundering, including Executive Order No. 13224 and the USA Patriot Act.

"**Applicable Law**" means all applicable provisions of constitutions, laws, statutes, ordinances, rules, treaties, regulations, permits, licenses, approvals, interpretations and orders of courts or Governmental Authorities and all orders and decrees of all courts and arbitrators.

"**Authorized Signer**" means any individual listed in Borrower's Borrowing Resolution who is authorized to execute the Loan Documents, including making (and executing if applicable) any Credit Extension request, on behalf of Borrower.

"**Bank**" is defined in the preamble hereof.

"**Bank Entities**" is defined in Section 11.8.

"**Bank Expenses**" are all documented audit fees, costs, and reasonable expenses (including reasonable, out-of-pocket and documented attorneys' fees and expenses) for preparing, amending, negotiating, administering, defending and enforcing the Loan Documents (including, without limitation, those incurred in connection with appeals or Insolvency Proceedings) or otherwise incurred with respect to Borrower or any Guarantor in connection with any Loan Document.

"**Bank Services**" are any products, credit services, and/or financial accommodations previously, now, or hereafter provided to Borrower or any of its Subsidiaries by Bank or any Bank Affiliate, including, without limitation, any letters of credit, cash management services (including, without limitation, merchant services, direct deposit of payroll, business credit cards, and check cashing services), interest rate swap arrangements, and foreign exchange services as any such products or services may be identified in Bank's various agreements related thereto (each, a "**Bank Services Agreement**").

"**Bank Services Agreement**" is defined in the definition of Bank Services.

"**Board**" is Borrower's board of directors or equivalent governing body.

"**Borrower**" is set forth on Schedule I hereto.

"**Borrower's Books**" are all Borrower's books and records including ledgers, federal and state tax returns, records regarding Borrower's assets or liabilities, the Collateral, business operations or financial condition, and all computer programs or storage or any equipment containing such information.

"**Borrowing Resolutions**" are, with respect to any Person, those resolutions adopted by such Person's board of directors (and, if required under the terms of such Person's Operating Documents, stockholders) and delivered by such Person to Bank approving the Loan Documents to which such Person is a party and the transactions contemplated thereby, together with a certificate executed by its secretary on behalf of such Person certifying (a) such Person has the authority to execute, deliver, and perform its obligations under each of the Loan Documents to which it is a party, (b) that set forth as a part of or attached as an exhibit to such certificate is a true, correct, and complete copy of the resolutions then in full force and effect authorizing and ratifying the execution, delivery, and performance by such Person of the Loan Documents to which it is a party, (c) the name(s) of the Person(s) authorized to execute the Loan Documents, including making (and executing if applicable) any Credit Extension request, on behalf of such Person, together with a sample of the true signature(s) of such Person(s), and (d) that Bank may conclusively rely on such certificate unless and until such Person shall have delivered to Bank a further certificate canceling or amending such prior certificate.

"**Business Day**" is a day other than a Saturday, Sunday or other day on which commercial banks in the State of California are authorized or required by law to close, except if any determination of a "Business Day" shall relate to an FX Contract, the term "Business Day" shall also mean a day on which dealings are carried on in the country of settlement of the Foreign Currency.

"**Cash Equivalents**" are (a) marketable direct obligations issued or unconditionally guaranteed by the United States or any agency or any State thereof having maturities of not more than one (1) year from the date of acquisition; (b) commercial paper maturing no more than one (1) year after its creation and having the highest rating from either Standard & Poor's Ratings Group or Moody's Investors Service, Inc.; (c) Bank's certificates of deposit issued maturing no more than one (1) year after issue; and (d) money market funds at least 95.0% of the assets of which constitute Cash Equivalents of the kinds described in clauses (a) through (c) of this definition.

"**Cayman Islands Electronic Signature Law**" is defined in Section 11.9.

"**Change in Control**" means (a) at any time, any "person" or "group" (as such terms are used in Sections 13(d) and 14(d) of the Exchange Act), shall become, or obtain rights (whether by means of warrants, options, or otherwise) to become, the "beneficial owner" (as defined in Rules 13(d)-3 and 13(d)-5 under the Exchange Act), directly or indirectly, of 49.0% or more of the ordinary voting power for the election of directors, partners, managers, and members, as applicable, of Borrower (determined on a fully diluted basis) other than by the sale of Borrower's equity securities in a public offering or to venture capital or private equity investors so long as Borrower identifies to Bank the venture capital or private equity investors at least seven (7) Business Days prior to the closing of the transaction and provides to Bank a description of the material terms of the transaction; (b) during any period of 12 consecutive months, a majority of the members of the Board of Borrower cease to be composed of individuals (i) who were members of that board or equivalent governing body on the first day of such period, (ii) whose election or nomination to that board or equivalent governing body was approved by individuals referred to in clause (i) above constituting at the time of such election or nomination at least a majority of that board or equivalent governing body, or (iii) whose election or nomination to that board or other equivalent governing body was approved by individuals referred to in clauses (i) and (ii) above constituting at the time of such election or nomination at least a majority of that board or equivalent governing body; or (c) at any time, Borrower shall cease to own and control, of record and beneficially, directly or indirectly, 100.0% of each class of outstanding stock, partnership, membership, or other ownership interest or other equity securities of each Subsidiary of Borrower free and clear of all Liens (except Permitted Liens).

"**Change in Law**" means the occurrence, after the Effective Date, of: (a) the adoption or taking effect of any law, rule, regulation, or treaty; (b) any change in Applicable Law or in the administration, interpretation, implementation, or application thereof by any Governmental Authority; or (c) the making or issuance of any request, rule, guideline, or directive (whether or not having the force of law) by any Governmental Authority; provided that, notwithstanding anything herein to the contrary, (i) the Dodd-Frank Wall Street Reform and Consumer Protection Act and all requests, rules, guidelines, or directives thereunder or issued in connection therewith and (ii) all requests, rules, guidelines, or directives promulgated by Bank for International Settlements, the Basel Committee on Banking Supervision (or any successor or similar authority), or the United States or foreign regulatory authorities, in each case pursuant to Basel III, shall in each case be deemed to be a "Change in Law", regardless of the date enacted, adopted, or issued.

"**Claims**" is defined in Section 11.3.

“**Code**” is the Uniform Commercial Code, as the same may, from time to time, be enacted and in effect in the Commonwealth of Massachusetts; provided, that, to the extent that the Code is used to define any term herein or in any Loan Document and such term is defined differently in different Articles or Divisions of the Code, the definition of such term contained in Article or Division 9 shall govern; provided further, that in the event that, by reason of mandatory provisions of law, any or all of the attachment, perfection, or priority of, or remedies with respect to, Bank’s Lien on any Collateral is governed by the Uniform Commercial Code in effect in a jurisdiction other than the Commonwealth of Massachusetts, the term “Code” shall mean the Uniform Commercial Code as enacted and in effect in such other jurisdiction solely for purposes of the provisions thereof relating to such attachment, perfection, priority, or remedies and for purposes of definitions relating to such provisions.

“**Collateral**” consists of all of Borrower’s right, title and interest in and to the following personal property:

(a) (i) all goods, Accounts (including health-care receivables), Equipment, Inventory, contract rights or rights to payment of money, leases, license agreements, franchise agreements, General Intangibles (except as provided below), commercial tort claims, documents, instruments (including any promissory notes), chattel paper (whether tangible or electronic), cash, deposit accounts, certificates of deposit, fixtures, letters of credit rights (whether or not the letter of credit is evidenced by a writing), securities, securities accounts, securities entitlements and all other investment property, supporting obligations, and financial assets, whether now owned or hereafter acquired, wherever located; and (ii) all Borrower’s Books relating to the foregoing, and any and all claims, rights and interests in any of the above and all substitutions for, additions, attachments, accessories, accessions and improvements to and replacements, products, proceeds and insurance proceeds of any or all of the foregoing.

(b) Notwithstanding the foregoing, the Collateral does not include (i) any Intellectual Property; provided, however, the Collateral shall include all Accounts and all proceeds of Intellectual Property; (ii) any interest of Borrower as a lessee or sublessee under a real property lease; (iii) rights held under a license that are not assignable by their terms without the consent of the licensor thereof (but only to the extent such restriction on assignment is enforceable under applicable law); (iv) any interest of Borrower as a lessee under an Equipment lease if Borrower is prohibited by the terms of such lease from granting a security interest in such lease or under which such an assignment or Lien would cause a default to occur under such lease; *provided, however,* that upon termination of such prohibition, such interest shall immediately become Collateral without any action by Borrower or Bank; and (v) any property to the extent that such grant of security interest is prohibited by any Applicable Law of a Governmental Authority or constitutes a breach or default under or results in the termination of or requires any consent not obtained under, any contract, license, agreement, instrument or other document evidencing or giving rise to such property, except to the extent that such Applicable Law or the term in such contract, license, agreement, instrument or other document providing for such prohibition, breach, default or termination or requiring such consent is ineffective under Section 9-406, 9-407, 9-408 or 9-409 of the Code (or any successor provision or provisions) of any relevant jurisdiction or any other applicable law (including the Bankruptcy Code) or principles of equity; provided, however, that such security interest shall attach immediately at such time as such Applicable Law is not effective or applicable, or such prohibition, breach, default or termination is no longer applicable or is waived, and to the extent severable, shall attach immediately to any portion of the Collateral that does not result in such consequences.

(c) Pursuant to the terms of a certain negative pledge arrangement with Bank, Borrower has agreed not to encumber any of its Intellectual Property without Bank’s prior written consent.

“**Collateral Account**” is any Deposit Account, Securities Account, or Commodity Account.

“**Commodity Account**” is any “commodity account” as defined in the Code, with such additions to such term as may hereafter be made.

“**Compliance Statement**” is that certain statement in the form attached hereto as Exhibit A.

“**Connection Income Taxes**” means Other Connection Taxes that are imposed on or measured by net income (however denominated) or that are franchise Taxes or branch profits Taxes.

"**Contingent Obligation**" is, for any Person, any direct or indirect liability of that Person for (a) any direct or indirect guaranty by such Person of any indebtedness, lease, dividend, letter of credit, credit card, or other obligation of another, (b) any other obligation endorsed, co-made, discounted or sold with recourse by that Person, or for which that Person is directly or indirectly liable; (c) any obligations for undrawn letters of credit for the account of that Person; and (d) all obligations from any interest rate, currency or commodity swap agreement, interest rate cap or collar agreement, or other agreement or arrangement designated to protect a Person against fluctuation in interest rates, currency exchange rates, or commodity prices; but "Contingent Obligation" does not include endorsements in the ordinary course of business. The amount of a Contingent Obligation is the stated or determined amount of the primary obligation for which the Contingent Obligation is made or, if not determinable, the maximum reasonably anticipated liability for it determined by the Person in good faith; but the amount may not exceed the maximum of the obligations under any guarantee or other support arrangement.

"**Control Agreement**" is any control agreement entered into among the depository institution at which Borrower maintains a Deposit Account or the securities intermediary or commodity intermediary at which Borrower maintains a Securities Account or a Commodity Account, Borrower, and Bank pursuant to which Bank obtains control (within the meaning of the Code) over such Deposit Account, Securities Account, or Commodity Account.

"**Copyrights**" are any and all copyright rights, copyright applications, copyright registrations and like protections in each work of authorship and derivative work thereof, whether published or unpublished and whether or not the same also constitutes a trade secret.

"**Credit Extension**" is any FX Contract, Term Loan Advance, or any other extension of credit by Bank for Borrower's benefit.

"**Default**" means any event which with notice or passage of time or both, would constitute an Event of Default.

"**Default Rate**" is defined in Section 1.2(c).

"**Deposit Account**" is any "**deposit account**" as defined in the Code with such additions to such term as may hereafter be made.

"**Designated Deposit Account**" is the deposit account established by Borrower with Bank for purposes of receiving Credit Extensions.

"**Division**" means, in reference to any Person which is an entity, the division of such Person into 2 or more separate Persons, with the dividing Person either continuing or terminating its existence as part of such division, including, without limitation, as contemplated under Section 18-217 of the Delaware Limited Liability Company Act for limited liability companies formed under Delaware law, Section 17-220 of the Delaware Revised Uniform Limited Partnership Act for limited partnerships formed under Delaware law, or any analogous action taken pursuant to any other Applicable Law with respect to any corporation, limited liability company, partnership or other entity.

"**Dollars**," "**dollars**" or use of the sign "$" means only lawful money of the United States and not any other currency, regardless of whether that currency uses the "$" sign to denote its currency or may be readily converted into lawful money of the United States.

"**Dollar Equivalent**" is, at any time, (a) with respect to any amount denominated in Dollars, such amount, and (b) with respect to any amount denominated in a Foreign Currency, the equivalent amount therefor in Dollars as determined by Bank at such time on the basis of the then-prevailing rate of exchange in San Francisco, California, for sales of the Foreign Currency for transfer to the country issuing such Foreign Currency.

"**Draw Period**" is set forth on Schedule I hereto.

"**Effective Date**" is set forth on Schedule I hereto.

"**Environmental Laws**" means any Applicable Law (including any permits, concessions, grants, franchises, licenses, agreements, or governmental restrictions) relating to pollution or the protection of health, safety, or the environment or the release of any materials into the environment (including those related to hazardous materials, air emissions, discharges to waste or public systems, and health and safety matters).

"**Equipment**" is all "equipment" as defined in the Code with such additions to such term as may hereafter be made, and includes without limitation all machinery, fixtures, goods, vehicles (including motor vehicles and trailers), and any interest in any of the foregoing.

"**Equity Event**" is set forth on Schedule I hereto.

"**ERISA**" is the Employee Retirement Income Security Act of 1974, as amended, and its regulations.

"**Event of Default**" is defined in Section 7.

"**Exchange Act**" is the Securities Exchange Act of 1934, as amended.

"**Excluded Taxes**" means any of the following Taxes imposed on or with respect to Bank or required to be withheld or deducted from a payment to Bank, (a) Taxes imposed on or measured by net income (however denominated), franchise Taxes, and branch profits Taxes, in each case, (i) imposed as a result of Bank being organized under the laws of, or having its principal office or its applicable lending office located in, the jurisdiction imposing such Tax (or any political subdivision thereof) or (ii) that are Other Connection Taxes, (b) U.S. federal withholding Taxes imposed on amounts payable to or for the account of Bank with respect to an applicable interest in a Credit Extension pursuant to a law in effect on the date on which (i) Bank acquires such interest in the Credit Extensions or (ii) Bank changes its lending office, except in each case to the extent that, pursuant to Section 1.6, amounts with respect to such Taxes were payable either to Bank's assignor immediately before Bank became a party hereto or to Bank immediately before it changed its lending office, (c) Taxes attributable to Bank's failure to comply with Section 1.6(e), and (d) any withholding Taxes imposed under FATCA.

"**FATCA**" means Sections 1471 through 1474 of the Internal Revenue Code, as of the date of this Agreement (or any amended or successor version that is substantively comparable and not materially more onerous to comply with), any current or future regulations or official interpretations thereof, any agreements entered into pursuant to Section 1471(b)(1) of the Internal Revenue Code and any fiscal or regulatory legislation, rules or practices adopted pursuant to any intergovernmental agreement, treaty or convention among Governmental Authorities and implementing such Sections of the Internal Revenue Code.

"**Final Payment**" is a one-time payment (in addition to and not a substitution for the regular monthly payments of principal plus accrued interest) due on the earliest to occur of (a) the Term Loan Maturity Date, (b) the repayment of the Term Loan Advances in full, (c) as required pursuant to Sections 1.1(c) or 1.1(d), or (d) the termination of this Agreement, in an amount equal to the aggregate original principal amount of the Term Loan Advances extended by Bank to Borrower multiplied by five percent (5.0)%.

"**Financial Statement Repository**" is NECreditSolutions@svb.com or such other means of collecting information approved and designated by Bank in connection with the Loan Documents after providing notice thereof to Borrower from time to time.

"**Foreign Currency**" is the lawful money of a country other than the United States.

"**Funding Date**" is any date on which a Credit Extension is made to or for the account of Borrower which shall be a Business Day.

"**FX Contract**" is any foreign exchange contract by and between Borrower and Bank under which Borrower commits to purchase from or sell to Bank a specific amount of Foreign Currency at a set price or on a specified date.

"**GAAP**" is generally accepted accounting principles set forth in the opinions and pronouncements of the Accounting Principles Board of the American Institute of Certified Public Accountants and statements and pronouncements of the Financial Accounting Standards Board or in such other statements by such other Person as may be approved by a significant segment of the accounting profession, which are applicable to the circumstances as of the date of determination.

"**General Intangibles**" is all "general intangibles" as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation, all Intellectual Property, claims, income and other tax refunds, security and other deposits, payment intangibles, contract rights, options to purchase or sell real or personal property, rights in all litigation presently or hereafter pending (whether in contract, tort or otherwise), insurance policies (including without limitation key man, property damage, and business interruption insurance), payments of insurance and rights to payment of any kind.

"**Governmental Approval**" is any consent, authorization, approval, order, license, franchise, permit, certificate, accreditation, registration, filing or notice, of, issued by, from or to, or other act by or in respect of, any Governmental Authority, including, without limitation, Healthcare Permits.

"**Governmental Authority**" is any nation or government, any state or other political subdivision thereof, any agency, authority, instrumentality, regulatory body, court, central bank or other entity exercising executive, legislative, judicial, taxing, regulatory or administrative functions of or pertaining to government, any securities exchange and any self-regulatory organization.

"**Guarantor**" is any Person providing a Guaranty in favor of Bank.

"**Guaranty**" is any guarantee of all or any part of the Obligations, as the same may from time to time be amended, restated, modified or otherwise supplemented.

"**Healthcare Laws**" means all applicable laws relating to the operation or management of hospitalist practices, the provision of hospitalist services, proper billing and collection practices relating to the payment for healthcare services, insurance law (including law related to payment for "no-fault" claims) and workers compensation law as they relate to the provision of, and billing and payment for, healthcare services, patient healthcare, patient healthcare information, patient abuse, the quality and adequacy of rehabilitative care, rate setting, equipment, personnel, operating policies, fee splitting, including, without limitation, (a) all federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute (42 U.S.C. §1320a-7b(b)), the Stark Law (42 U.S.C. §1395nn), the civil False Claims Act (31 U.S.C. §3729 et seq.), the administrative False Claims Law (42 U.S.C. § 1320a-7b(a)), the Anti-Inducement Law (42 U.S.C. § 1320a-7a(a)(5)), the exclusion laws (42 U.S.C. § 1320a-7); (b) the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009; (c) the Medicare Regulations and the Medicaid Program (Title XIX of the Social Security Act); (d) quality, safety and accreditation standards and requirements of all applicable state laws or regulatory bodies; (e) all laws, policies, procedures, requirements and regulations pursuant to which Healthcare Permits are issued; (f) any laws, regulations or administrative guidance with respect to fee splitting by healthcare professionals and the corporate practice of medicine in any jurisdiction in which any Borrower or any Guarantor operates; and (g) any and all comparable state or local laws and other applicable health care laws, regulations, manual provisions, policies and administrative guidance, each of (a) through (g) as may be amended from time to time and the regulations promulgated pursuant to each such law.

"**Healthcare Permit**" means, with respect to any Person, a permit issued or required under Healthcare Laws applicable to the business of Borrower or any Guarantor, or necessary in the possession, ownership, warehousing, marketing, promoting, sale, labeling, furnishing, distribution or delivery of goods or services under Healthcare Laws applicable to the business of Borrower or any Guarantor.

"**HIPAA**" means, collectively, the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic Clinical Health (HITECKH) Act and the implementing regulations thereto.

"**Indebtedness**" is (a) indebtedness for borrowed money or the deferred price of property or services, such as reimbursement and other obligations for surety bonds and letters of credit, (b) obligations evidenced by notes, bonds, debentures or similar instruments, (c) capital lease obligations, (d) Contingent Obligations and (e) other short- and long-term obligations under debt agreements, lines of credit and extensions of credit.

"**Indemnified Person**" is defined in Section 11.3.

"**Indemnified Taxes**" means (a) Taxes, other than Excluded Taxes, imposed on or with respect to any payment made by or on account of any obligation of Borrower under any Loan Document and (b) to the extent not otherwise described in clause (a), Other Taxes.

"**Information**" is defined in Section 11.8.

"**Insolvency Proceeding**" is any proceeding by or against any Person under the United States Bankruptcy Code, or any other bankruptcy or insolvency law, including assignments for the benefit of creditors, compositions, extensions generally with its creditors, or proceedings seeking reorganization, arrangement, receivership or other relief.

"**Intellectual Property**" means, with respect to any Person, all of such Person's right, title, and interest in and to the following:

(a) its Copyrights, Trademarks and Patents;

(b) any and all trade secrets and trade secret rights, including, without limitation, any rights to unpatented inventions, know-how and operating manuals;

(c) any and all source code;

(d) any and all design rights which may be available to such Person;

(e) any and all claims for damages by way of past, present and future infringement of any of the foregoing, with the right, but not the obligation, to sue for and collect such damages for said use or infringement of the Intellectual Property rights identified above; and

(f) all amendments, renewals and extensions of any of the Copyrights, Trademarks or Patents.

"**Internal Revenue Code**" means the U.S. Internal Revenue Code of 1986, and the rules and regulations promulgated thereunder, each as amended or modified from time to time.

"**Inventory**" is all "**inventory**" as defined in the Code in effect on the date hereof with such additions to such term as may hereafter be made, and includes without limitation all merchandise, raw materials, parts, supplies, packing and shipping materials, work in process and finished products, including without limitation such inventory as is temporarily out of Borrower's custody or possession or in transit and including any returned goods and any documents of title representing any of the above.

"**Investment**" is any beneficial ownership interest in any Person (including stock, partnership, membership, or other ownership interest or other equity securities), and any loan, advance or capital contribution to any Person.

"**Key Person**" is each of Borrower's (i) Chief Executive Officer, who is Dan Passeri, (ii) Chief Scientific Officer, who is Anish Suri, and (iii) Chief Financial Officer, who is Kerri-Ann Millar.

"**Letter of Credit**" is a standby or commercial letter of credit issued by Bank upon request of Borrower based upon an application, guarantee, indemnity, or similar agreement.

"**Lien**" is a claim, mortgage, deed of trust, levy, attachment charge, pledge, hypothecation, security interest or other encumbrance of any kind, whether voluntarily incurred or arising by operation of law or otherwise against any property.

"**Loan Documents**" are, collectively, this Agreement and any schedules, exhibits, certificates, notices, and any other documents related to this Agreement, the Perfection Certificate, the Stock Pledge Agreement, any Control Agreements, any Bank Services Agreement, any subordination agreement, any note, or notes or guaranties executed by Borrower or any Guarantor, landlord waivers and consents, bailee waivers and consents, and any other present or future agreement by Borrower and/or any Guarantor with or for the benefit of Bank in connection with this Agreement or Bank Services, all as amended, restated, or otherwise modified in accordance with the terms thereof.

"**Material Adverse Change**" is (a) a material impairment in the perfection or priority of Bank's Lien in the Collateral or in the value of such Collateral; (b) a material adverse change in the business, operations, or condition (financial or otherwise) of Borrower; or (c) a material impairment of the prospect of repayment of any portion of the Obligations.

"**Obligations**" are Borrower's obligations to pay when due any debts, principal, interest, fees, Bank Expenses, the Final Payment, the Prepayment Fee, and other amounts Borrower owes Bank now or later, whether under this Agreement, the other Loan Documents, or otherwise, including, without limitation, all obligations relating to Bank Services and interest accruing after Insolvency Proceedings begin and debts, liabilities, or obligations of Borrower assigned to Bank, and to perform Borrower's duties under the Loan Documents.

"**OFAC**" is the Office of Foreign Assets Control of the United States Department of the Treasury and any successor thereto.

"**Operating Documents**" are, for any Person, such Person's formation documents, as certified by the Secretary of State (or equivalent agency) of such Person's jurisdiction of organization on a date that is no earlier than 30 days prior to the Effective Date, and, (a) if such Person is a corporation, its bylaws in current form, (b) if such Person is a limited liability company, its limited liability company agreement (or similar agreement), and (c) if such Person is a partnership or limited partnership, its partnership agreement or limited partnership agreement (or similar agreement), each of the foregoing with all current amendments or modifications thereto.

"**Other Connection Taxes**" means, with respect to Bank, Taxes imposed as a result of a present or former connection between Bank and the jurisdiction imposing such Tax (other than connections arising from Bank having executed, delivered, become a party to, performed its obligations under, received payments under, received or perfected a security interest under, engaged in any other transaction pursuant to, or enforced any Loan Document, or sold or assigned an interest in any Credit Extension or Loan Document).

"**Other Taxes**" means all present or future stamp, court, documentary, intangible, recording, filing or similar Taxes that arise from any payment made under, from the execution, delivery, performance, enforcement or registration of, from the receipt or perfection of a security interest under, or otherwise with respect to, any Loan Document, except any such Taxes that are Other Connection Taxes imposed with respect to an assignment.

"**Patents**" means all patents, patent applications, and like protections including without limitation improvements, divisions, continuations, renewals, reissues, extensions, and continuations-in-part of the same.

"**Payment/Advance Form**" is that certain form in the form attached hereto as Exhibit B.

"**Payment Date**" is set forth on Schedule I hereto.

"**Perfection Certificate**" is the Perfection Certificate delivered by Borrower in connection with this Agreement, as may be updated from time to time pursuant to the terms herein.

"**Permitted American Express Credit Cards**" are defined in clause (j) of Permitted Indebtedness.

“**Permitted Indebtedness**” is:

(a) Borrower’s Indebtedness to Bank under this Agreement and the other Loan Documents;

(b) Indebtedness existing on the Effective Date which is shown on the Perfection Certificate;

(c) Subordinated Debt;

(d) unsecured Indebtedness to trade creditors incurred in the ordinary course of business;

(e) Indebtedness incurred as a result of endorsing negotiable instruments received in the ordinary course of business;

(f) Indebtedness secured by Liens permitted under clauses (a) and (c) of the definition of “Permitted Liens” hereunder;

(g) Indebtedness consisting of the financing of insurance premiums;

(h) other unsecured Indebtedness not otherwise permitted by Section 7.4 in an aggregate amount not to exceed $100,000.00 at any time;

(i) intercompany Indebtedness permitted as a Permitted Investment;

(j) unsecured Indebtedness in connection with Borrower’s existing credit card facilities with American Express (collectively, the “**Permitted American Express Credit Cards**”), in an aggregate amount not to exceed $75,000.00 at any time; and

(k) extensions, refinancings, modifications, amendments and restatements of any items of Permitted Indebtedness (a) through (j) above, provided that the principal amount thereof is not increased or the terms thereof are not modified to impose more burdensome terms upon Borrower or its Subsidiary, as the case may be.

“**Permitted Investments**” are:

(a) Investments (including, without limitation, Subsidiaries) existing on the Effective Date which are shown on the Perfection Certificate;

(b) cash Investments by Borrower in Securities Corp.; provided that an Event of Default does not exist at the time of any such Investment, and would not exist after giving effect to any such Investment;

(c) Investments consisting of Cash Equivalents;

(d) Investments consisting of the endorsement of negotiable instruments for deposit or collection or similar transactions in the ordinary course of Borrower;

(e) Investments consisting of deposit accounts (but only to the extent that Borrower is permitted to maintain such accounts pursuant to Section 5.7 of this Agreement) in which Bank has a first priority perfected security interest;

(f) joint ventures or strategic alliances consisting of the development of and/or commercialization of product candidates and/or products, provided that any cash investments by Borrower do not exceed $200,000.00 in the aggregate in any fiscal year;

(g) Investments consisting of (i) travel advances and employee relocation loans and other employee loans and advances in the ordinary course of business, and (ii) loans to employees, officers, directors, partners, managers and members relating to the purchase of equity securities of Borrower or its Subsidiaries pursuant to employee equity purchase plans or similar agreements approved by the Board;

(h) Investments (including debt obligations) received in connection with the bankruptcy or reorganization of customers or suppliers and in settlement of delinquent obligations of, and other disputes with, customers or suppliers arising in the ordinary course of business;

(i) Investments consisting of notes receivable of, or prepaid royalties and other credit extensions, to customers and suppliers who are not Affiliates, in the ordinary course of business; provided that this paragraph (i) shall not apply to Investments of Borrower in any Subsidiary;

(j) Investments by one Borrower or secured Guarantor in another Borrower or secured Guarantor;

(k) other Investments not otherwise permitted by Section 6.7 in an aggregate amount not to exceed $100,000.00 at any time; and

(l) Investments accepted in connection with Transfers permitted by this Agreement.

"**Permitted Liens**" are:

(a) Liens existing on the Effective Date which are shown on the Perfection Certificate or arising under this Agreement or the other Loan Documents;

(b) Liens for taxes, fees, assessments or other government charges or levies, either (i) not due and payable or (ii) being contested in good faith and for which Borrower maintains adequate reserves on Borrower's Books, provided that no notice of any such Lien has been filed or recorded under the Internal Revenue Code;

(c) purchase money Liens (i) on Equipment acquired or held by Borrower incurred for financing the acquisition of the Equipment securing no more than $250,000.00 in the aggregate amount outstanding, or (ii) existing on Equipment when acquired, if the Lien is confined to the property and improvements and the proceeds of the Equipment;

(d) Liens of carriers, warehousemen, suppliers, or other Persons that are possessory in nature arising in the ordinary course of business so long as such Liens attach only to Inventory, securing liabilities in the aggregate amount not to exceed $25,000.00 and which are not delinquent or remain payable without penalty or which are being contested in good faith and by appropriate proceedings which proceedings have the effect of preventing the forfeiture or sale of the property subject thereto;

(e) Liens to secure payment of workers' compensation, employment insurance, old-age pensions, social security and other like obligations incurred in the ordinary course of business (other than Liens imposed by ERISA);

(f) leases or subleases of real property granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), and leases, subleases, non-exclusive licenses or sublicenses of personal property (other than Intellectual Property) granted in the ordinary course of Borrower's business (or, if referring to another Person, in the ordinary course of such Person's business), if the leases, subleases, licenses and sublicenses do not prohibit granting Bank a security interest therein;

(g) non-exclusive licenses of Intellectual Property granted to third parties in the ordinary course of business, and licenses of Intellectual Property that could not result in a legal transfer of title of the licensed property that may be exclusive in respects other than territory and that may be exclusive as to territory only as to one or more discrete geographical areas outside of the United States;

(h) Liens arising from attachments or judgments, orders, or decrees in circumstances not constituting an Event of Default under Sections 7.4 and 7.7;

(i) Liens comprised of security deposits favor of landlord(s) of premises rented by Borrower or its Subsidiaries in an aggregate amount not to exceed $4,375,000.00 at any time;

(j) Liens arising from the filing of any precautionary financing statement on operating leases covering the leased property, to the extent such operating leases are permitted under this Agreement;

(k) easements, rights-of-way, restrictions and other similar encumbrances affecting real property which, in the aggregate, are not substantial in amount, and which do not in any case materially detract from the value of the property subject thereto or materially interfere with the ordinary conduct of the business of the applicable Person;

(l) Liens on insurance proceeds granted solely as security for financed insurance premiums solely to the extent such Indebtedness secured thereby is permitted under clause (g) of the definition of Permitted Indebtedness; and

(m) Liens incurred in the extension, renewal or refinancing of the Indebtedness secured by Liens described in (a) through (l), but any extension, renewal or replacement Lien must be limited to the property encumbered by the existing Lien and the principal amount of the indebtedness may not increase.

"**Person**" is any individual, sole proprietorship, partnership, limited liability company, joint venture, company, trust, unincorporated organization, association, corporation, institution, public benefit corporation, firm, joint stock company, estate, entity or government agency.

"**Prepayment Fee**" shall be an additional fee, payable to Bank, with respect to each Term Loan Advance, in an amount equal to:

(a) for a prepayment of the Term Loan Advances made on or prior to the first (1st) anniversary of the Effective Date, three percent (3.0%) of the aggregate original principal amount of the Term Loan Advances immediately prior to the date of such prepayment;

(b) for a prepayment of the Term Loan Advances made after the first (1st) anniversary of the Effective Date, but on or prior to the second (2^{nd}) anniversary of the Effective Date, two percent (2.0%) of the aggregate original principal amount of the Term Loan Advances immediately prior to the date of such prepayment; and

(c) for a prepayment of the Term Loan Advances made after the second (2^{nd}) anniversary of the Effective Date, but prior to the Term Loan Maturity Date, one percent (1.0%) of the aggregate original principal amount of the Term Loan Advances immediately prior to the date of such prepayment.

Notwithstanding the foregoing, provided no Event of Default has occurred and is continuing, the Prepayment Fee shall be waived by Bank, if Bank closes on the refinance and redocumentation of the Term Loan Advances (in its sole and absolute discretion) prior to the Term Loan Maturity Date.

"**Prime Rate**" is set forth on Schedule I hereto.

"**Prime Rate Margin**" is set forth on Schedule I hereto.

"**Registered Organization**" is any "registered organization" as defined in the Code with such additions to such term as may hereafter be made.

"**Repayment Schedule**" is set forth on Schedule I hereto.

"**Representatives**" is defined in Section 11.8.

"**Responsible Officer**" is any of the Chief Executive Officer, President, Chief Financial Officer and Controller of Borrower.

"**Restricted License**" is any material license or other material agreement with respect to which Borrower is the licensee (a) that prohibits or otherwise restricts Borrower from granting a security interest in Borrower's interest in such license or agreement or any other property, or (b) for which a default under or termination of could interfere with Bank's right to sell any Collateral.

"**Sanctioned Person**" means a Person that: (a) is listed on any Sanctions list maintained by OFAC or any similar Sanctions list maintained by any other Governmental Authority having jurisdiction over Borrower; (b) is located, organized, or resident in any country, territory, or region that is the subject or target of Sanctions; or (c) is 50.0% or more owned or controlled by one (1) or more Persons described in clauses (a) and (b) hereof.

"**Sanctions**" means the economic sanctions laws, regulations, embargoes or restrictive measures administered, enacted or enforced by the United States government and any of its agencies, including, without limitation, OFAC and the U.S. State Department, or any other Governmental Authority having jurisdiction over Borrower.

"**SEC**" is the Securities and Exchange Commission, any successor thereto, and any analogous Governmental Authority.

"**Securities Account**" is any "securities account" as defined in the Code with such additions to such term as may hereafter be made.

"**Securities Corp.**" is Cue Biopharma Securities Corp., a corporation organized under the laws of the Commonwealth of Massachusetts and a Subsidiary of Borrower.

"**Stock Pledge Agreement**" means that certain Stock Pledge Agreement executed by Borrower in favor of Bank dated as of Effective Date, as may be amended, modified, supplemented or restated from time to time.

"**Subordinated Debt**" is indebtedness incurred by Borrower or any of its Subsidiaries subordinated to all of Borrower's or any of its Subsidiaries' now or hereafter indebtedness to Bank (pursuant to a subordination, intercreditor, or other similar agreement in form and substance satisfactory to Bank entered into between Bank and the other creditor), on terms acceptable to Bank.

"**Subsidiary**" is, as to any Person, a corporation, partnership, limited liability company or other entity of which shares of stock, partnership, membership, or other ownership interest or other equity securities having ordinary voting power (other than stock, partnership, membership, or other ownership interest or other equity securities having such power only by reason of the happening of a contingency) to elect a majority of the board of directors or other managers of such corporation, partnership or other entity are at the time owned, or the management of which is otherwise controlled, directly or indirectly through one or more intermediaries, or both, by such Person. Unless the context otherwise requires, each reference to a Subsidiary herein shall be a reference to a Subsidiary of Borrower or Guarantor.

"**Taxes**" means all present or future taxes, levies, imposts, duties, deductions, withholdings (including backup withholding), assessments, fees or other charges imposed by any Governmental Authority, including any interest, additions to tax or penalties applicable thereto.

"**Term A Loan Advance**" is defined in Section 1.1.

"**Term A Loan Availability Amount**" is set forth on Schedule I hereto.

"**Term B Loan Advance**" and "**Term B Loan Advances**" are each defined in Section 1.1.

"**Term B Loan Availability Amount**" is set forth on Schedule I hereto.

“**Term Loan Advance**” and “**Term Loan Advances**” are each defined in Section 1.1.

“**Term Loan Amortization Date**” is set forth on Schedule I hereto.

“**Term Loan Maturity Date**” is set forth on Schedule I hereto.

“**Trademarks**” means, with respect to any Person, any trademark and servicemark rights, whether registered or not, applications to register and registrations of the same and like protections, and the entire goodwill of the business of such Person connected with and symbolized by such trademarks.

“**Transfer**” is defined in Section 6.1.

“**USA Patriot Act**” means the “Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001” (Public Law 107-56, signed into law on October 26, 2001), as amended from time to time.

[Signature page follows]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed as a sealed instrument under the laws of the Commonwealth of Massachusetts as of the Effective Date.

BORROWER:

CUE BIOPHARMA, INC.

By: /s/ Kerri-Ann Millar

Name: Kerri-Ann Millar

Title: Chief Financial Officer

BANK:

SILICON VALLEY BANK

By: /s/ John Sansone

Name: John Sansone

Title: Vice President

SCHEDULE I
LSA PROVISIONS

LSA Section	**LSA Provision**
1.1(a) – Term Loan – Availability	Each Term B Loan Advance must be in an amount equal to at least $5,000,000.00. After repayment, no Term Loan Advance (or any portion thereof) may be reborrowed.
1.1(b) – Term Loan – Repayment	Commencing on the Term Loan Amortization Date and continuing on each Payment Date thereafter, Borrower shall repay each Term Loan Advance in accordance with the Repayment Schedule, plus monthly payments of accrued interest at the rate set forth in Section 1.2(b)(i).
1.2(a) – Interest Payments – Term Loan Advances	Interest on the principal amount of each Term Loan Advance is payable in arrears monthly (A) on each Payment Date commencing on the first Payment Date following the Funding Date of each such Term Loan Advance, (B) on the date of any prepayment and (C) on the Term Loan Maturity Date.
1.2(b)(i) – Interest Rate – Term Loan Advances	The outstanding principal amount of any Term Loan Advance shall accrue interest at a floating rate per annum equal to the greater of (1) five and one half of one percent (5.5%), and (2) the Prime Rate plus the Prime Rate Margin, which interest shall be payable in accordance with Section 1.2(a).
1.2(e) – Interest Computation	Interest shall be computed on the basis of the actual number of days elapsed and a 360-day year for any Credit Extension outstanding.
12.2 – "Borrower"	"**Borrower**" means **CUE BIOPHARMA, INC.**, a Delaware corporation.
12.2 – "Draw Period"	"**Draw Period**" is the period commencing upon the occurrence of (i) the Equity Event and (ii) Milestone Event and ending on the earlier to occur of (a) December 31, 2022, and (b) an Event of Default.
12.2 – "Effective Date"	"**Effective Date**" is February 15, 2022.
12.2 – "Equity Event"	"**Equity Event**" occurs if and when (if ever) Bank confirms in writing, after the Effective Date, but on or prior to December 31, 2022, that Borrower has received, after the Effective Date, but on or prior to December 31, 2022, unrestricted and unencumbered net cash proceeds in an amount equal to at least $[**] from the issuance and sale by Borrower of its equity securities to investors acceptable to Bank.
12.2 – "Milestone Event"	"**Milestone Event**" occurs if and when (if ever) Bank confirms in writing, after the Effective Date, but on or prior to December 31, 2022, that it has received evidence, satisfactory to Bank in its sole and absolute discretion, that Borrower has achieved positive final data from CUE-101 Phase 1 Part B monotherapy sufficient to begin a Phase 2 clinical trial.
12.2 – "Payment Date"	"**Payment Date**" is the first (1st) calendar day of each month.

12.2 – "Prime Rate"	"**Prime Rate**" is the rate of interest per annum from time to time published in the money rates section of The Wall Street Journal or any successor publication thereto as the "prime rate" then in effect; provided that if such rate of interest, as set forth from time to time in the money rates section of The Wall Street Journal, becomes unavailable for any reason as determined by Bank, the "Prime Rate" shall mean the rate of interest per annum announced by Bank as its prime rate in effect at its principal office in the State of California (such Bank announced Prime Rate not being intended to be the lowest rate of interest charged by Bank in connection with extensions of credit to debtors); provided that, in the event such rate of interest is less than zero percent (0.0%) per annum, such rate shall be deemed to be zero percent (0.0%) per annum for purposes of this Agreement.
12.2 – "Prime Rate Margin"	"**Prime Rate Margin**" is two and one quarter of one percent (2.25%).
12.2 – "Repayment Schedule"	"**Repayment Schedule**" means the period of time equal to 30 consecutive months, which shall be decreased to 24 consecutive months upon the funding of the Term B Loan Advances in the aggregate principal amount equal to the Term B Loan Availability Amount.
12.2 – "Term A Loan Availability Amount"	"**Term A Loan Availability Amount**" is an original principal amount equal to $10,000,000.00.
12.2 – "Term B Loan Availability Amount"	"**Term B Loan Availability Amount**" is an aggregate original principal amount equal to $10,000,000.00.
12.2 – "Term Loan Amortization Date"	"**Term Loan Amortization Date**" is July 1, 2023, which shall be extended to January 1, 2024 upon the funding of the Term B Loan Advances in the aggregate principal amount equal to the Term B Loan Availability Amount.
12.2 – "Term Loan Maturity Date"	"**Term Loan Maturity Date**" is December 1, 2025.

SUBSIDIARIES OF CUE BIOPHARMA, INC.

Registrant's consolidated subsidiaries are shown below, together with the state or jurisdiction of organization of each subsidiary and the percentage of voting securities that Registrant owns in each subsidiary.

Name of Subsidiary	Jurisdiction of Incorporation or Organization	Percent of Outstanding Voting Securities Owned
Cue Biopharma Securities Corp.	Massachusetts	100%

EXHIBIT 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statements (Nos. 333-229140 and 333-23957) on Form S-3 and Registration Statements (Nos. 333-224018, 333-230282 and 333-237140) on Form S-8 of Cue Biopharma, Inc. of our report dated March 16, 2022, relating to the consolidated financial statements of Cue Biopharma, Inc. and Subsidiary appearing in this Annual Report on Form 10-K of Cue Biopharma, Inc. for the year ended December 31, 2021.

/s/ RSM US LLP

Boston, Massachusetts
March 16, 2022

EXHIBIT 31.1

CERTIFICATION OF THE PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Daniel R. Passeri, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cue Biopharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2022

/s/ Daniel R. Passeri
Name: Daniel R. Passeri
Title: Chief Executive Officer
(Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Kerri-Ann Millar, certify that:

1. I have reviewed this Annual Report on Form 10-K of Cue Biopharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

    a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

    b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

    c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

    d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 16, 2022

/s/ Kerri-Ann Millar

Name: Kerri-Ann Millar
Title: Chief Financial Officer
(Principal Financial Officer and Principal Accounting Officer)

EXHIBIT 32.1

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

In connection with the Annual Report on Form 10-K of Cue Biopharma, Inc. (the “Company”) for the year ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the “Report”), we, Daniel R. Passeri, Chief Executive Officer of the Company, and Kerri-Ann Millar, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, to our knowledge that:

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

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

A signed original of this written statement required by Section 906 has been provided to Cue Biopharma, Inc. and will be retained by Cue Biopharma, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

/s/ Daniel R. Passeri	/s/ Kerri-Ann Millar
Name: Daniel R. Passeri	Name: Kerri-Ann Millar
Title: Chief Executive Officer (Principal Executive Officer)	Title: Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)
Date: March 16, 2022	Date: March 16, 2022