2022 ANNUAL REPORT

NASDAQ: XLO

xilio THERAPEUTICS®

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

FORM 10-K

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

For the fiscal year ended December 31, 2022

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from _____ to _____.

Commission file number: 001-40925

XILIO THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**85-1623397**
(State of Other Jurisdiction of incorporation or Organization)	(I.R.S. Employer Identification No.)
828 Winter Street, Suite 300, Waltham, MA	**02451**
(Address of principal executive offices)	(Zip code)

Registrant's telephone number, including area code: (857) 524-2466

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

Title of Class	*Trading Symbols*	*Name of Exchanges on Which Registered*
Common stock, par value $0.0001 per share	**XLO**	**Nasdaq Global Select 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 (§232.0405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 232.405 of this chapter) is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

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

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

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

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

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

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

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

As of June 30, 2022, the last day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the common stock held by non-affiliates of the registrant was approximately $70.4 million based on the closing price of the registrant's common stock on June 30, 2022.

The number of shares of the registrant's common stock outstanding as of February 24, 2023 was 27,471,740.

Documents Incorporated by Reference

Portions of the registrant's definitive proxy statement for its 2023 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A within 120 days after the end of the registrant's fiscal year ended December 31, 2022, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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References to Xilio

Unless otherwise stated, all references to "us," "our," "we," "Xilio," "Xilio Therapeutics," "the Company" and similar references in this Annual Report on Form 10-K refer to Xilio Therapeutics, Inc. and its consolidated subsidiaries. Xilio Therapeutics and its associated logos are registered trademarks of Xilio Therapeutics, Inc. Other brands, names and trademarks contained in this Annual Report on Form 10-K are the property of their respective owners.

Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "aim," "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," or the negative of these words or other comparable terminology, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the initiation, timing, progress and results of our research and development programs and preclinical studies and clinical trials;
- our plans to develop and, if approved, subsequently commercialize any product candidates we may develop;
- the timing of and our ability to submit applications for, and obtain and, if approved, maintain regulatory approvals for our product candidates;
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash and cash equivalents;
- the potential advantages and benefits of our current and future product candidates;
- the rate and degree of market acceptance of our product candidates, if approved;
- our estimates regarding the addressable patient population and potential market opportunity for our current and future product candidates;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates;
- our ability to identify additional products, 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 and expectations regarding developments and projections relating to our current or future competitors and any competing therapies that are or become available;
- developments relating to our competitors and our industry;

- our ability to establish and maintain collaborations or obtain additional funding;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act;
- the impact of general economic conditions, including inflation; and
- the impact of public health crises, including epidemics and pandemics such as the COVID-19 pandemic, on our business, operations, strategy, goals and anticipated milestones, as well as our response to such epidemics or pandemics.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly those described in the "Risk Factor Summary" and "Risk Factors" section in Part I, Item 1A of this Annual Report on Form 10-K, that could cause actual results or events to differ materially from the forward-looking statements that we make. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make or enter into.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results, performance or achievements may be materially different from what we expect. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

Risk Factor Summary

Our business is subject to numerous risks that, if realized, could materially and adversely affect our business, financial condition, results of operations and future growth prospects. These risks are discussed more fully in Part I, Item 1A. "Risk Factors" in this Annual Report on Form 10-K. These risks include, but are not limited to, the following:

- We will need to obtain substantial additional capital to finance our operations and complete the development and any commercialization of any current or future product candidates. If we are unable to raise this capital when needed, we may be forced to delay, reduce or eliminate one or more of our research and development programs or other operations.
- Our business is highly dependent on the success of our current product candidates, which are in the early stages of development and will require significant additional preclinical and clinical development before we can seek regulatory approval for and commercially launch a product.
- Our approach to the discovery and development of product candidates based on our technological approaches is unproven, and we do not know whether we will be able to develop any products of commercial value.
- Preclinical development is uncertain. Our preclinical programs may experience delays or may never advance to clinical trials, which would adversely affect our ability to obtain regulatory approvals or commercialize these programs on a timely basis or at all, which would have an adverse effect on our business.
- We may encounter substantial delays in the commencement or completion, or termination or suspension, of our clinical trials, which could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

- Our product candidates may cause undesirable or unexpectedly severe side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

- Interim top-line and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

- We expect to develop certain of our product candidates in combination with third-party drugs and we will have limited or no control over the safety, supply, regulatory status or regulatory approval of such drugs.

- Manufacturing biologics is complex, and we may experience manufacturing problems that result in delays in our development or commercialization programs.

- We face risk related to our reliance on our current and any future third-party contract manufacturers, or CMOs. For example, the CMOs on which we rely may not continue to meet regulatory requirements, may have limited capacity and may experience interruptions in supply, any of which could adversely affect our development and commercialization plans for our product candidates.

- We expect to rely on third parties to conduct, supervise and monitor IND-enabling studies and clinical trials, and if these third parties perform in an unsatisfactory manner, it may harm our business, reputation and results of operations.

- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

- If we are unable to obtain and maintain patent protection for any product candidates we develop or for other proprietary technologies we may develop, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize product candidates and technology similar or identical to our product candidates and technology, and our ability to successfully commercialize any product candidates we may develop, and our technology may be adversely affected.

- We rely on in-license agreements for patent rights with respect to our product candidates and may in the future acquire or in license additional third-party intellectual property rights on which we may similarly rely. We face risks with respect to such reliance, including the risk that we could lose these rights that are important to our business if we fail to comply with our obligations under these licenses or that we may be unable to acquire or in license third party intellectual property that may be necessary or important to our business operations.

PART I

Item 1. Business

Overview

We are a clinical-stage biotechnology company discovering and developing tumor-activated immuno-oncology, or I-O, therapies with the goal of significantly improving outcomes for people living with cancer without the systemic side effects of current I-O treatments. We are leveraging our proprietary geographically precise solutions, or GPS, platform to build a pipeline of novel, tumor-activated molecules, including cytokines and other biologics, which are designed to optimize their therapeutic index by localizing anti-tumor activity within the tumor microenvironment. Current I-O therapies have curative potential for patients with cancer; however, their potential is significantly curtailed by systemic toxicity that results from activity of the therapeutic molecule outside the tumor microenvironment. Our molecules are engineered to localize activity within the tumor microenvironment with minimal systemic effects, resulting in the potential to achieve enhanced anti-tumor activity and increasing the population of patients who may be eligible to receive our medicines. Our most advanced tumor-activated, clinical-stage product candidates are XTX202, an interleukin 2, or IL-2, therapy, XTX301, an interleukin 12, or IL-12, therapy and XTX101, an Fc-enhanced, anti-CTLA-4 monoclonal antibody, or mAb. In addition to our clinical-stage product candidates, we are continuing to leverage our GPS platform and expertise in developing tumor-activated I-O therapies as we seek to expand our pipeline of discovery-stage programs and develop additional tumor-activated immunotherapies, including product candidates with a range of tumor targeting approaches.

XTX202 is an investigational tumor-activated beta-gamma biased (non-alpha), engineered IL-2 molecule designed to potently stimulate CD8+ effector T cells and natural killer, or NK, cells without concomitant stimulation of regulatory T cells when activated (unmasked) in the tumor microenvironment. We are currently evaluating XTX202 in an ongoing Phase 1 clinical trial in patients with advanced solid tumors. The Phase 1 trial is a first-in-human, multi-center, open-label trial designed to evaluate the safety and tolerability of multiple ascending doses of XTX202 with the goal of establishing a recommended Phase 2 dose, or RP2D, for XTX202 as a monotherapy in patients with advanced solid tumors. We recently completed dosing patients at the 1 mg/kg dose level (dose level four) and are currently enrolling patients at the 1.4 mg/kg dose level (dose level five) in monotherapy dose-escalation (Part 1A) of the clinical trial. Importantly, no signs of vascular leak syndrome, or VLS, including hypotension or decreases in albumin (an early sign of VLS) or hemodynamic compromise, have been observed in patients to date. Monotherapy dose expansion (Part 1B) of the Phase 1 clinical trial is open for enrollment, and we plan to initiate patient enrollment in a Phase 2 clinical trial evaluating XTX202 as a monotherapy in patients with unresectable or metastatic melanoma and metastatic renal cell carcinoma, or RCC, in April 2023. In addition, we plan to report preliminary anti-tumor activity, safety, pharmacokinetic, or PK, and pharmacodynamic, or PD, data from the Phase 1/2 clinical trial in the third quarter of 2023, which we anticipate will include approximately 15-20 patients across a range of solid tumors treated at the 1 mg/kg dose or higher across all cohorts in the Phase 1/2 clinical trial.

XTX301 is an investigational tumor-activated, engineered IL-12 molecule designed to potently stimulate anti-tumor immunity and reprogram the tumor microenvironment of poorly immunogenic "cold" tumors towards an inflamed, or "hot," state. In November 2022, we announced clearance of our investigational new drug application, or IND, by the U.S. Food and Drug Administration, or FDA, for XTX301 for evaluation in patients with advanced solid tumors. We recently opened clinical trial sites and are actively screening patients for enrollment at a starting dose of 5.0 µg/kg (0.005 mg/kg) in monotherapy dose-escalation for our Phase 1 clinical trial evaluating the safety and tolerability of XTX301 in patients with advanced solid tumors. We anticipate reporting preliminary safety data from the Phase 1 clinical trial into at least the third dose level in the fourth quarter of 2023.

XTX101 is an investigational Fc-enhanced, tumor-activated anti-CTLA-4 mAb designed to deplete regulatory T cells when activated (unmasked) in the tumor microenvironment and improve upon the therapeutic index of existing anti-CTLA-4 therapies. We are currently evaluating XTX101 in an ongoing Phase 1 clinical trial in patients with advanced solid tumors. The Phase 1 clinical trial is a first in-human, multi-center, open-label trial designed to evaluate the safety and tolerability of XTX101 for the treatment of adult patients with advanced solid tumors. We recently completed enrollment in monotherapy dose-escalation (Part 1A) of the Phase 1 trial, and enrollment in monotherapy dose-expansion (Part 1B) of the Phase 1 trial is ongoing. In addition, we have determined an RP2D of 150 mg once every six weeks, or Q6W. We

anticipate reporting preliminary safety, PK, PD and anti-tumor activity data from the Phase 1 clinical trial in the second quarter of 2023. As previously announced, we plan to continue to explore strategic opportunities to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

In addition to our most advanced product candidates, we believe our proprietary GPS platform has the potential to develop additional product candidates using a range of approaches to achieve tumor-activation and derive a clinically meaningful improvement in therapeutic index.

We currently have worldwide development and commercialization rights to all of our product candidates.

Our Approach—Improving the Therapeutic Index of I-O Therapies

Our focus is to improve upon two of the foundational mechanisms of I-O: cytokines and checkpoint inhibitors. Since the 1980s, cytokines have been explored as a cancer therapy due to their ability to carry messages between cells and serve as master regulators of the body's response to inflammation and immune attack. Although cytokines have demonstrated compelling clinical efficacy in certain tumors, including the ability to generate sustained complete responses, or CRs, in a subset of patients, their use has been limited by severe systemic toxicity. Similar to cytokines, checkpoint inhibitors have shown the potential to provide meaningful improvements in survival for patients with cancer, but the utilization of these therapies, beyond those that target the immune proteins PD(L)-1, is also limited largely by toxicity.

Our goal is to overcome the limitations of current I-O therapies by developing products with an improved efficacy-to-toxicity ratio, or therapeutic index. The toxicities for cytokines and checkpoint inhibitors stem from their activity outside of the tumor microenvironment. Our GPS platform is designed to overcome these systemic toxicities by creating tumor-activated molecules and unleashing the activity of cytokines and checkpoint inhibitors in the tumor microenvironment. These molecules are intended to be inactive until they reach the tumor microenvironment, where they are activated, resulting in localized clinical activity with minimal dose-limiting toxicities. To achieve this tumor selectivity, we apply our GPS platform, which includes engineered features and a proprietary protein masking technology that render our molecules inactive until reaching the tumor. Our GPS platform also enables PK and protease-dependent activation, resulting in geographically localized anti-tumor activity. The engineered features are designed to ensure that our product candidates are stable molecules with well-understood properties and a reproducible manufacturing approach.

Leveraging our GPS platform, we intend to develop a number of additional product candidates using a range of tumor targeting approaches, with the goal of achieving a clinically meaningful improvement in their therapeutic index. We also plan to evaluate opportunities for better tolerated and more efficacious combination therapies, using product candidates from across our portfolio with other cancer therapies, to increase the potential for curative regimens in oncology. Beyond oncology, we also plan to apply our GPS platform to other disease areas in which the immune system is dysregulated, such as in autoimmune and inflammatory diseases.

Our Strategy

Our vision is to transform the lives of patients with cancer by harnessing the power of highly potent, tumor-selective I-O therapies that deliver deep and durable clinical responses. By leveraging our GPS platform, we aim to discover, develop and, ultimately, commercialize I-O therapies that overcome the known limitations of today's approaches and provide effective, tolerable and durable therapeutic options for patients and their physicians.

In order to achieve these goals, the key elements of our strategy are to:

- **Efficiently progress XTX202, our tumor-activated IL-2, through initial Phase 1 clinical proof-of-concept data, and if successful, expand clinical development for multiple cancer indications as a monotherapy and in combination with other therapies, including in combination with XTX301, our tumor-activated IL-12.** XTX202 is a tumor-activated beta-gamma biased (non-alpha), engineered IL-2 molecule designed to potently stimulate CD8+ effector T cells and NK cells without concomitant stimulation of regulatory T cells when activated (unmasked) in the tumor microenvironment. We are currently evaluating XTX202 as a monotherapy in an ongoing Phase 1 clinical trial in patients with advanced solid tumors, and we anticipate initiating patient

enrollment in a Phase 2 clinical trial evaluating XTX202 as a monotherapy in patients with unresectable or metastatic melanoma and metastatic RCC in April 2023. In addition, we plan to report preliminary anti-tumor activity, safety, PK and PD data from the Phase 1/2 clinical trial in the third quarter of 2023, which we anticipate will include approximately 15-20 patients across a range of solid tumors treated at the 1 mg/kg dose or higher across all cohorts in the Phase 1/2 clinical trial. Subject to these interim trial results and establishing initial clinical proof-of-concept for XTX202, we plan to complete the Phase 2 trial evaluating XTX202 as monotherapy in patients with RCC and melanoma with the goal of determining the potential to conduct monotherapy registration-enabling trials for XTX202. In parallel to the completion of the planned Phase 2 monotherapy trial, we plan to initiate a Phase 1/2 trial evaluating XTX202 in combination with an anti-PD-1/PD-L1 for the treatment of patients with non-small cell lung cancer, or NSCLC. Subject to the results from this combination study, we anticipate initiating registration-enabling clinical trials for XTX202 in combination with an anti-PD-1/PD-L1 in patients with NSCLC. We also plan to explore the potential for XTX202 in combination with other therapies, including combinations with XTX301, our tumor-activated IL-12, and potential collaborations with cell therapies or anti-cancer vaccines.

- **Efficiently progress XTX301, our tumor-activated IL-12, through initial Phase 1 monotherapy dose-escalation, and if successful, expand clinical development for multiple "hot" and "cold" tumors as a monotherapy and in combination with other therapies.** IL-12 plays a key role in bridging innate and adaptive cellular immunity, making it a compelling target for immunotherapy. However, life-threatening toxicity observed with systemically active IL-12, including severe liver toxicity, have limited the therapeutic potential of IL-12 agents. XTX301, our tumor-activated IL-12, is designed to potently stimulate anti-tumor immunity and reprogram the tumor microenvironment of poorly immunogenic "cold" tumors towards an inflamed, or "hot," state. We recently opened clinical trial sites and are actively screening patients for enrollment at a starting dose of 5.0 μg/kg (0.005 mg/kg) in monotherapy dose-escalation for our Phase 1 clinical trial evaluating the safety and tolerability of XTX301 in patients with advanced solid tumors. We anticipate reporting preliminary safety data from the Phase 1 clinical trial into at least the third dose level in the fourth quarter of 2023. Subject to achieving a minimal target dose, we would continue monotherapy dose-escalation of the Phase 1 clinical trial and initiate treatment in cohorts of patients with both "cold" and "hot" tumors to determine the potential for anti-tumor activity. Following an assessment of anti-tumor effect as a monotherapy in selected tumor types, we also plan to explore the combination potential of XTX301 with an anti-PD-1/PD-L1 and with XTX202, our tumor-activated IL-2 product candidate, prior to initiation of registration-enabling clinical trials. Subject to the successful completion of trials showing the ability to combine XTX301 with other I-O agents and immune activation in "cold" tumors, we would plan to explore potential registration-enabling trials in both "hot" tumors, such as head and neck cancer and NSCLC, and in "cold" tumors, such as microsatellite stable colorectal cancer, or MSS CRC, and pancreatic cancer.

- **Report Phase 1 monotherapy data for XTX101 and explore strategic opportunities to advance XTX101 with a partner.** We are currently evaluating XTX101 in an ongoing Phase 1 clinical trial in patients with advanced solid tumors. We recently completed enrollment in monotherapy dose-escalation (Part 1A) of the Phase 1 trial, and enrollment in monotherapy dose-expansion (Part 1B) of the Phase 1 trial is ongoing. In addition, we have determined an RP2D of 150 mg Q6W, and we anticipate reporting preliminary safety, PK, PD and anti-tumor activity data from the Phase 1 clinical trial in the second quarter of 2023. As previously announced, we plan to continue to explore strategic opportunities to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

- **Broadly expand our portfolio by applying the versatility and reproducibility of our GPS platform to develop novel I-O therapies for cancer.** We have prioritized efforts to develop novel I-O therapies based on the therapeutic activity of I-O agents established in other clinical trials, while recognizing that the benefit of many of these I-O agents, particularly cytokines, has been historically hampered by issues of short half-life, poor bioavailability and significant toxicity. By leveraging the insights and capabilities of our GPS platform and our leadership team, we aim to systematically create novel molecules, including cytokines, mAbs and multi-functional biologics, that overcome these challenges to safely localize their potent activity to the tumor microenvironment. We believe that our GPS platform, which enables us to develop molecules with the potential to trigger anti-tumor immunity while limiting systemic exposure to improve tolerability, is broadly applicable in oncology and has the potential to develop a number of additional product candidates using a range of tumor targeting approaches, with the goal of achieving a clinically meaningful improvement in their therapeutic index.

- **Build a fully-integrated I-O company by independently commercializing approved products in indications and key geographies where we believe we can maximize our product candidates' value.** We currently own all worldwide development and commercialization rights to our product candidates and programs, which we believe have been optimally selected based on our extensive preclinical data, including data with disease-specific animal models and biomarkers, supporting their potential for clinical success. To maximize the full potential and value of our pipeline, we intend to retain key development and commercialization rights for our product candidates in key indications and geographies where we believe we can ultimately commercialize successfully on our own, if approved. In addition, we intend to pursue strategic collaborations where a collaborator may have geographic operations or other capabilities that are synergistic or additive to our own.

- **Leverage the broad applicability of our GPS platform through strategic collaborations in autoimmune diseases.** We believe the collective components of our GPS platform and the reproducibility it enables in our drug discovery and development efforts present a meaningful opportunity for us to leverage our GPS platform not only in oncology but also in multiple therapeutic areas beyond oncology, such as in autoimmune and inflammatory diseases. We plan to explore strategic collaborations that would enable us to accelerate the development of additional product candidates or programs as well as expand our capabilities, pipeline opportunities and product offerings, particularly where a collaborator may have expertise or capabilities that are synergistic or additive to our own.

About I-O

The discovery of a role for immunotherapy in the treatment of cancer was made more than 100 years ago, when William Coley treated patients with heat-treated bacterial toxins, resulting in a profound anti-tumor effect in some of those patients. Two of the most important mechanisms within I-O are cytokines and checkpoint inhibitors, with cytokine therapies having been introduced in the 1980s and checkpoint inhibitors in the period after 2011, when the first such product was approved. Both therapeutic approaches are known to provide efficacy in terms of clinical responses and tumor shrinkage. However, toxicities have limited the application of these therapies, resulting in the need to dose-reduce, dose-interrupt or discontinue many patients from treatment. Immune checkpoint inhibitors are associated with immune-related adverse events, or AEs, that may affect any organ system and may be life-threatening or fatal to patients. Cytokines in particular are associated with broad ranging multi-organ toxicities that can be lethal and have limited the development of this class of potential therapies. Anti-PD-1/PD-L1 checkpoint inhibitors have been used broadly because they generally achieve efficacy with minimal systemic toxicity, enabling their administration at their maximally effective doses. Anti-PD-1/PD-L1 treatments have become the most widely utilized immunotherapy agent in oncology, with FDA approvals in more than a dozen separate tumor types and $27 billion in worldwide sales in 2020. Our mission is to overcome the limitations of cytokine therapies and checkpoint inhibitors, such as anti-CTLA-4, and make immunotherapies beyond anti-PD-1/PD-L1 treatments more accessible, efficacious and safe for patients with cancer.

The promise and limitations of cytokines

Cytokines are small signaling proteins that serve as master regulators of the body's response to inflammation and immune attack. There are multiple cytokines, including IL-2, which are approved in a range of oncology and non-oncology indications. Aldesleukin, a high-dose IL-2 therapy, was first approved in 1992 as a monotherapy for patients with

melanoma and RCC. In addition, cytokines have shown potential beyond oncology with approvals for the treatment of patients with multiple sclerosis, resulting in cytokines becoming a key treatment option for a range of conditions. However, cytokines have not achieved therapeutic success in a broad population of patients because their use has been limited by severe toxicity, including fatal outcomes. We believe XTX202, our tumor-activated IL-2 product candidate, and XTX301, our tumor-activated IL-12 product candidate, each have the potential to overcome these limitations and deliver a therapeutic dose with low systemic toxicity and the ability to achieve a broad therapeutic index.

The promise and limitations of checkpoint inhibitors

Checkpoint inhibitors have become mainstays in cancer therapy since the FDA approved ipilimumab, an anti-CTLA-4 therapy, in 2011. Similar to cytokines, checkpoint inhibitors have shown the potential to provide meaningful improvements in survival for patients with cancer, but the utilization of these therapies has been limited largely by toxicities. These toxicities, which can be life-threatening or fatal, have resulted in the need to dose-reduce, dose-interrupt or discontinue many patients from treatment. To date, anti-PD-1/PD-L1 checkpoint inhibitors have been used broadly due to their ability to achieve efficacy with minimal systemic toxicity, enabling their administration at their maximally effective doses. In contrast, while the clinical benefit of CTLA-4 blockade to patients with cancer is well-established, the efficacy of current CTLA-4 therapies is impaired by dose-limiting toxicities arising from systemic immune activation. This has reduced the use of anti-CTLA-4 mAbs both as a monotherapy and in combination therapy. We believe XTX101, our Fc-enhanced, tumor-activated anti-CTLA-4, has the potential to overcome these limitations and deliver the full clinical benefit of anti-CTLA-4 mechanisms without the dose-limiting toxicities associated with existing CTLA-4 treatments.

I-O Combinations

The ability to combine oncology agents has been an important step in developing effective cancer regimens. Combination chemotherapy can be curative in settings where single agents have had limited efficacy and were not considered curative. The substantial dose-limiting toxicities associated with I-O agents has prevented these agents from being combined effectively. The ultimate promise of I-O for patients is dependent upon the ability to develop I-O agents that can be combined at their optimal doses without life-threatening toxicity. The severe toxicity of IL-2 has limited the ability to combine IL-2 with other cancer treatments without compromising the dose administered. Similarly, data from third-party clinical trials has demonstrated that the combination of ipilimumab, an anti-CTLA-4 therapy, with nivolumab, which targets the immune checkpoint protein PD-1, was associated with improved clinical outcomes, but it was limited by significantly higher risk of all-grade and high-grade immune-related AEs such as pruritus, rash, diarrhea, colitis, elevation of the liver enzyme alanine transaminase, known as ALT, hyperthyroidism, hypophysitis and pneumonitis. Importantly, combination therapy generally requires use of low dose ipilimumab at 1 mg/kg rather than the more efficacious dose of 10 mg/kg. Even at the lower dose, ipilimumab combination therapy is poorly tolerated, with AEs causing up to 80% of patients to discontinue treatment, up to 50% of patients requiring emergency room visits and up to 36% of patients requiring hospitalization. The potential of our tumor-activated molecules to minimize the systemic toxicity of I-O could allow us to combine I-O agents to meaningfully improve survival in a broader range of tumor types.

Our Solution: Our GPS Platform Enables Tumor-Activated I-O Molecules Designed to Optimize Their Therapeutic Index

I-O therapies have curative potential for patients with cancer. However, this potential has been significantly curtailed to date by dose-limiting toxicities that result from activity of the therapeutic molecule outside the tumor microenvironment. We believe that geographic localization of the activity of I-O agents to the tumor microenvironment can overcome these dose-limiting toxicities and enable maximal therapeutic benefit for patients. Tumor-selective activation could be achieved by harnessing unique characteristics of the tumor microenvironment to activate therapeutic molecules locally that have minimal or non-detectable levels of activity outside of the tumor microenvironment.

Matrix metalloproteases, or MMPs, are enzymes involved in protein degradation that are essential for tumor growth and metastasis because they regulate key processes within the tumor microenvironment, including tumor growth, angiogenesis, invasion and metastasis. MMPs are dysregulated in the tumor microenvironment, resulting in preferential activity of MMPs in the tumor microenvironment by comparison to non-tumor, healthy tissues. As a result, we believe that our GPS platform,

which is designed to harness tumor MMP activity, can activate our molecules selectively within the tumor microenvironment while maintaining minimal or non-detectable levels of activity outside of the tumor microenvironment.

Our GPS platform enables us to engineer a broad range of immune-modulatory molecules, including cytokines, antibodies and multi-functional molecules, that contain masking domains designed to minimize their activity outside of the tumor microenvironment and turn on selectively in the tumor microenvironment where they are preferentially activated by tumor MMPs. Specifically, MMPs enzymatically cleave a protease cleavage site incorporated in a peptide linker that connects the masking protein domain to the active agent. This separates the mask from the active agent, enabling the unmasked agent to promote an anti-tumor response within the tumor microenvironment.

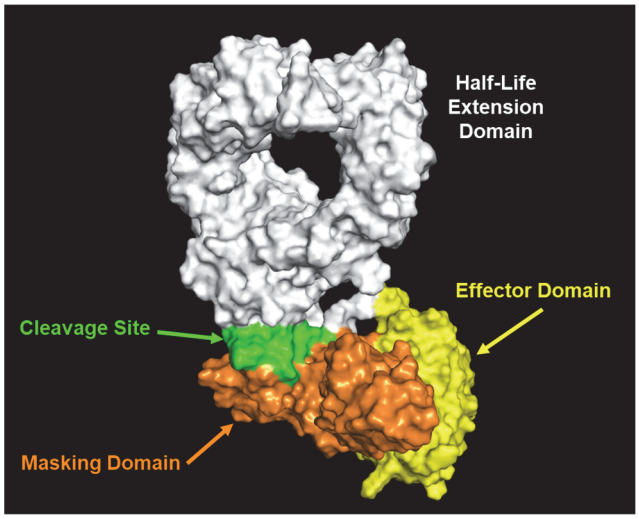
Key features of our tumor-activated molecules exemplify the engineering approach that underpins our GPS platform. Each feature contributes to multiple characteristics of the molecule that are designed to enable tumor selective biological activity and tumor growth inhibition while minimizing toxicity outside of the tumor microenvironment. The general architecture of each of our tumor-activated molecules is:

- a masking domain;
- linker sequences;
- a protease cleavage site;
- a half-life extension domain for cytokine molecules, as appropriate; and
- the active engineered molecule (i.e., an engineered cytokine or antibody).

The engineered features are designed to ensure that our product candidates are stable molecules with well-understood properties and a reproducible manufacturing approach. In preclinical studies, we have successfully applied our GPS platform to cytokines, antibodies that regulate immune checkpoints and multi-functional molecules in order to promote localized anti-tumor immune responses, while avoiding the dose-limiting toxicities associated with systemic immune responses.

The graphic below illustrates XTX202, our tumor-activated IL-2, which contains a masking domain that is released by protease cleavage. When the linker sequence, which contain a protease cleavage site, is cleaved by proteases, the masking domain is released, allowing the cytokine to bind to the target receptor. Before cleavage by the MMP in the tumor microenvironment, the engineered cytokine has minimal or non-detectable levels of activity outside the tumor microenvironment. Specifically, there is no binding to target receptors, and the molecule has a long half-life outside the tumor microenvironment. After cleavage in the tumor microenvironment, the engineered cytokine is locally activated and has a relatively short half-life.

Key Features of Xilio's Tumor-Activated Cytokines



We believe that the characteristics of our GPS platform described above enable the following key advantages:

- masking that takes advantage of multiple intra-molecular interactions, minimizing the risk of activity outside of the tumor microenvironment and therefore minimizing the risk of toxicity;
- engineering the active molecule such that unmasking in the tumor microenvironment promotes a potent, localized anti-tumor immune response;
- early consideration and incorporation of manufacturing and development aspects into the design of molecules to facilitate production of high-quality drug product for clinical use;
- half-life extending inactive (masked) cytokines, as appropriate, to support administration to patients on a schedule consistent with other biologics agents; and
- locally activating cytokine molecules that have a short half-life in the tumor microenvironment, which minimizes the risk of the released cytokine exhibiting activity outside of the tumor microenvironment and, therefore, further reduces the risk of toxicity.

We have shown preclinical validation and promising early clinical evidence of the ability of our GPS platform to develop tumor-activated cytokines and antibodies. In preclinical studies, each of our most advanced product candidates exhibited tumor-activated biological activity, tumor growth inhibition and minimal to no toxicity outside of the tumor microenvironment. The reproducibility of these preclinical data highlights the potential breadth of application of our GPS platform to multiple structurally diverse cytokines, antibodies and multi-functional molecules. In our Phase 1 trial for XTX202, our tumor-activated IL-2, we have demonstrated initial clinical validation of our GPS platform, as evidenced by preliminary intratumoral PD data for two patients treated with XTX202, each of whom had an optional on-treatment tumor biopsy and were the only two patients from whom a tumor biopsy analysis was available as March 1, 2023. For each patient, the tumor sample featured increased numbers of stromal tumor infiltrating lymphocytes, or TILs, and increased frequency of CD8+ effector T cells among these TILs. At the time of the tumor sample, these changes occurred in each patient in the absence of peripheral changes to CD8+ effector T cells, demonstrating preliminary evidence of tumor-selective activation. We believe our GPS platform can be applied to numerous molecules, which have potential as cancer therapies, but require localized activity within the tumor microenvironment to overcome the dose-limiting toxicities that result from activity outside of the tumor microenvironment.

Our Pipeline

Leveraging our GPS platform, we are building a pipeline of tumor-activated cytokine, checkpoint inhibitor and multi-functional immunotherapies to treat cancer. Our goal is to overcome the limitations of current I-O therapies by developing products with an improved therapeutic index. Consistent with this goal, we selected molecules that have prior clinical validation demonstrating therapeutic benefit, but that have been limited by significant toxicities that we believe can be addressed with our approach. We currently have worldwide development and commercialization rights to all of our product candidates.

Program	Disease Indication	Mechanism of Action	Stage of Development
Cytokine Programs			
XTX202 [(1)]	Oncology	IL-2	Phase 1 monotherapy dose-escalation (Part 1A) ongoing and monotherapy dose expansion (Part 1B) open for enrollment
XTX301 [(2)]	Oncology	IL-12	Phase 1 clinical trial sites open and actively screening patients for enrollment
Undisclosed Research Program	Oncology	Tumor-Activated Multi-Functional	Discovery stage
Antibody Program			
XTX101 [(3)]	Oncology	anti-CTLA-4	Enrollment in Phase 1 monotherapy dose-escalation (Part 1A) complete; Phase 1 monotherapy dose-expansion (Part 1B) ongoing

1. Plan to initially evaluate XTX202 as a monotherapy in patients with melanoma and RCC prior to evaluating XTX202 in combination with an anti-PD-1/PD-L1 for the treatment of patients with NSCLC or potential expansion into additional cancer indications as a monotherapy or combination therapy.
2. Plan to initially evaluate XTX301 as a monotherapy in patients with advanced solid tumors.
3. Plan to explore opportunities for strategic collaborations to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

Our development strategy for our clinical-stage, tumor-activated cytokine product candidates is focused on the following:

(1) achieve an acceptable safety profile while maintaining dose levels sufficient to confer localized anti-tumor activity in the tumor microenvironment;

(2) achieve clinical proof-of-mechanism for our GPS platform by showing tumor-selective activation, as demonstrated by increased tumor fighting immune cells in patient tumors, including CD8+ effector T cells and NK cells, without an increase in tumor fighting immune cells in the periphery;

(3) establish clinical proof-of-concept for each product candidate, as demonstrated by monotherapy anti-tumor activity in patients treated at the target dose level for such product candidate; and

(4) demonstrate the ability to administer our product candidates in combination with other therapies, so they can be explored and administered with relevant standard-of-care agents to potentially improve patient outcomes.

Assuming we successfully achieve an improved therapeutic index during our initial clinical trials, we plan to proceed into an expansive set of registration-enabling clinical trials across a range of tumor types.

Cytokine Programs

The major focus in our cytokine programs is the development of tumor-activated cytokines with exemplary clinical activity and tolerability. These cytokine programs include our clinical-stage, tumor-activated product candidates, XTX202 (IL-2) and XTX301 (IL-12), as well as discovery-stage programs for oncology and autoimmune diseases.

XTX202, Our Clinical-Stage, Tumor-Activated IL-2 Product Candidate

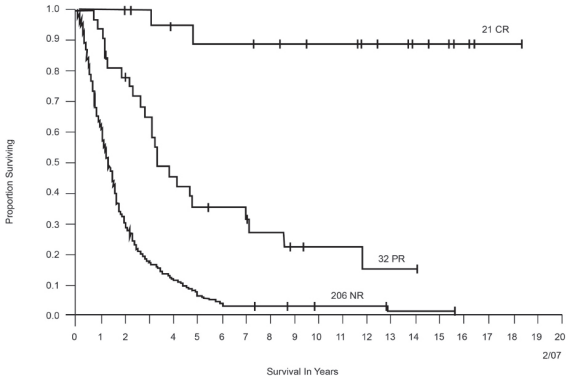
XTX202 is an investigational tumor-activated beta-gamma biased (non-alpha), engineered IL-2 molecule designed to potently stimulate CD8+ effector T cells and NK cells without concomitant stimulation of regulatory T cells when activated (unmasked) in the tumor microenvironment. We are currently evaluating XTX202 as a monotherapy in an ongoing Phase 1 clinical trial in patients with advanced solid tumors. For more information, please see the sections entitled "—Clinical Development Plans for XTX202" and "—Phase 1 Clinical Trial for XTX202" below.

Background on IL-2

IL-2: Extensive clinical evidence of the promise and limitations of cytokines

As shown in the figure below, high-dose IL-2 has resulted in long-term survival in a subset of patients who had achieved a CR. We believe that patients who develop a CR when treated with high-dose IL-2 are highly likely to achieve a long-term durable response or cure.

Survival of Patients Who Achieved a CR with High-Dose IL-2



Historical use of IL-2 in cancer has been accompanied by severe toxicity

The power of IL-2 is promising, but it has been greatly reduced due to toxicities. When administered locally, IL-2 has been shown to be clinically active and well-tolerated, shrinking local cancerous lesions and reducing malignant effusions. However, when administered systemically, treatment with IL-2 has been shown to induce severe toxicities, including VLS, myocardial infarction, or heart attack, acute renal failure and immune-mediated neuropathy. This toxicity profile greatly limits its current use.

In order to localize IL-2, many groups have tried linking IL-2 to tumor-targeting mAbs, creating fusion proteins. These fusion proteins can accumulate in a tumor and create locally high IL-2 concentrations. However, the use of cytokine fusion proteins has not prevented systemic toxicity because the long circulating half-life of antibody fusions and unexpected cleavage of IL-2 from the antibody domain has contributed to high systemic IL-2 levels in some cases.

The toxicities associated with early IL-2 therapies, such as aldesleukin, are hypothesized to be associated in part with binding and signaling through the high affinity αβγ IL-2receptor on immune cells or vascular endothelial cells. In addition, the αβγ IL-2receptor is expressed at high levels on regulatory T cells, or TREGs, which act to inhibit the immune response, whereas the intermediate affinity βγ IL-2 receptor is expressed on cells that promote immune response including CD8+ effector T cells and NK cells.

Modeling of IL-2 activity in preclinical animal tumor models and evaluation of dosage and dose-frequency data from patients has suggested that IL-2 has a steep dose-activity curve, with reduced exposure impacting both efficacy and toxicity. IL-2 anti-tumor activity and toxicity are both dependent on the amount of IL-2 administered. Therefore, in order

to provide the greatest benefit to patients, the goal is to engineer a form of IL-2 that can minimize systemic effects while harnessing and directing activity to the tumor microenvironment.

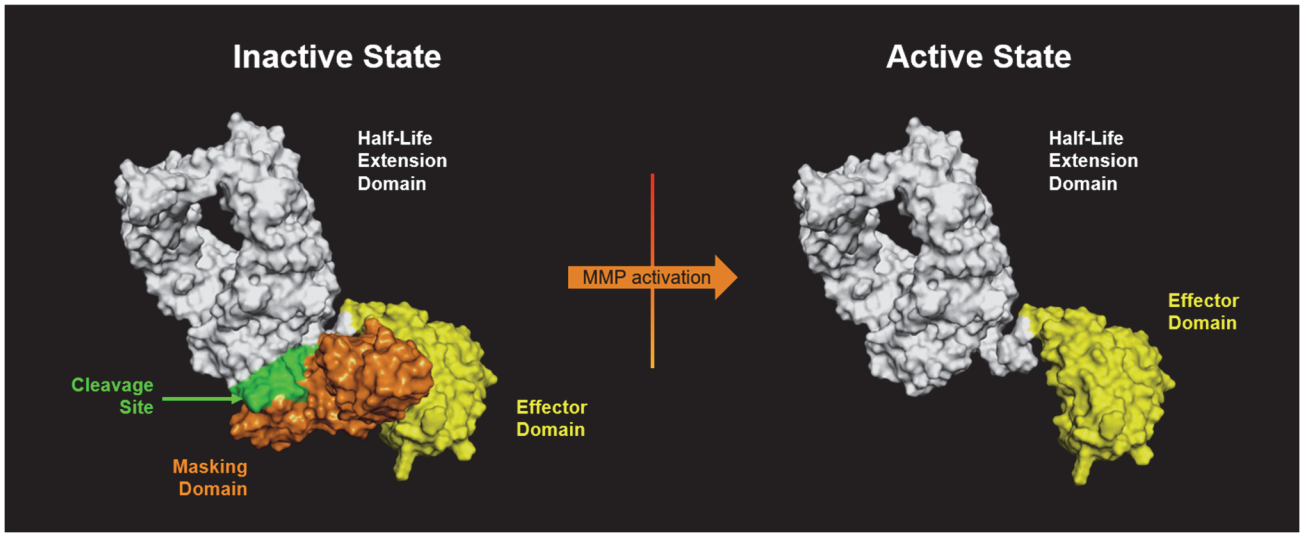
Rationale for non-alpha IL-2

The application of cytokines to treat cancer fits with the role these signaling molecules have evolved to play in the body. Many key cytokines, including IL-2, regulate the immune system, and it is now recognized that there are immune stimulatory cytokines, immune suppressive cytokines and cytokines that have multiple activities on different target cell types. IL-2 is a master regulator of immune responses and has been investigated extensively as a potential anti-cancer immunotherapy. IL-2 supports the function, survival and proliferation of T cells, including the subset of T cells known as CD8+ effector T cells that are most closely linked to anti-tumor immunity.

The activities of IL-2 are driven by two classes of receptor complexes, which are present on different T cell subsets. The high-affinity αβγ receptor present primarily on TREGs, and the intermediate-affinity βγ receptor present primarily on CD8+ effector T cells and NK cells. In contrast to wild-type IL-2, XTX202 does not bind the α-subunit of the IL-2 receptor and therefore does not induce the preferential activity on TREGs that limits the immune activating effect of wild type IL-2. XTX202 is designed to potently stimulate CD8+ effector T cells and NK cells that express the βγ receptor.

Our Solution: XTX202, a Tumor-Activated IL-2

The critical challenge in the development of IL-2 therapies is to improve patient tolerability without reducing efficacy. Deploying the key structural components of our GPS platform, we have designed XTX202 with three key features designed to overcome this: (1) avoidance of binding to CD25, the IL-2α receptor subunit, in order to reduce the activation of Treg cells that inhibit immune response, while maintaining effective activation of CD8+ and NK cells that promote an anti-tumor immune response; (2) overcoming the short circulating half-life of the native cytokine using the half-life extension domain; and (3) a removable protease-cleavable protein mask that prevents XTX202 from binding and signaling until the mask is removed by the MMPs that are preferentially active within the tumor microenvironment.



These key features are intended to ensure that XTX202 is released and activated preferentially within the tumor microenvironment, where it has been designed to bind to lymphocytes. In the tumor microenvironment, XTX202 is designed to be unmasked and to bind to the IL-2 βγ receptors that are abundantly expressed on CD8+ effector T cells and NK cells, activating these cells. Locally activated T cells and NK cells have potent anti-tumor cytotoxic activity. The unmasked XTX202 is then rapidly internalized by these lymphocytes, shortening the systemic half-life of the active (unmasked) molecule and localizing its activity to the tumor.

Overview of preclinical studies and data

We have undertaken extensive preclinical studies to demonstrate the two key characteristics of XTX202: (1) anti-tumor activity and (2) minimal or no evidence of systemic toxicity. In order to assess this, we compared XTX202 to both aldesleukin and a non-masked version of the molecule, which we refer to as XTX200, a non-α IL-2 with the same half-life extension domain feature but no mask to block IL-2 function systemically. XTX200 also serves as a surrogate for other non-α IL-2 molecules currently being investigated by others. This was done to assess the activity of our masking technology and compare XTX202 against high-dose IL-2. We believe that these studies collectively provide preclinical proof-of-concept with an improved therapeutic index due to tumor microenvironment-dependent activation of XTX202 that, if replicated in clinical trials, could result in significant benefits to patients with a variety of cancer types. The key findings of our XTX202 preclinical studies are as follows:

- XTX202 demonstrated minimal signaling through the IL-2 receptor when masked, and MMP activation of XTX202 restored full potency of IL-2 signaling in *in vitro* assays illustrating the tight, protease-dependent control of IL-2 activity conferred by XTX202;

- XTX202 activated an immune response in the tumor but not in peripheral organs, demonstrating geographically selective tumor PD activity *in vivo* in mice;

- XTX202 matched the tumor growth inhibition activity of XTX200 and aldesleukin, without activation of immune response outside of the tumor microenvironment, thereby avoiding the systemic toxicity (VLS and enlargement of the spleen, or splenomegaly), body weight loss and mortality in mice that were associated with the doses of XTX200 or aldesleukin required for tumor growth inhibition;

- XTX202 was well-tolerated in non-human primates, or NHPs, with no evidence of VLS or systemic immune activation in non-tumor, healthy tissue, whereas XTX200 induced both; and

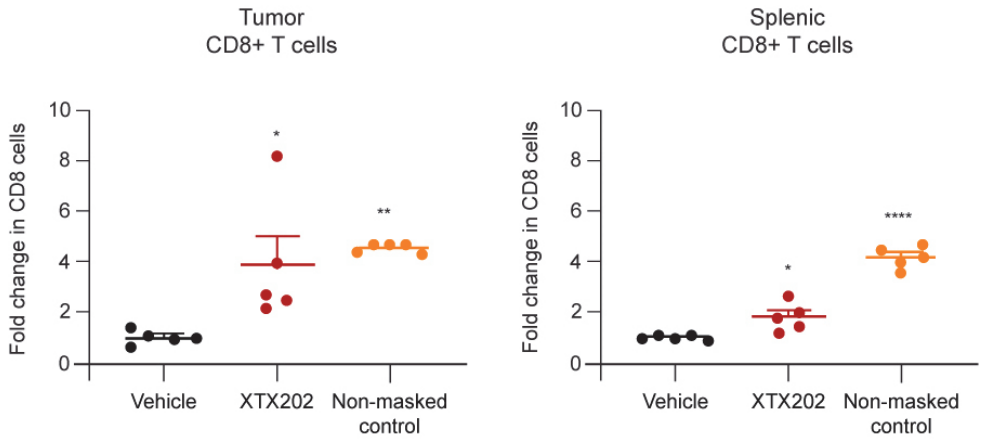
- XTX202 exhibited a half-life of greater than one week in NHPs, compared to a half-life of less than 0.5 days for XTX200. Based on these data, we believe that circulating levels of masked XTX202 can be achieved with clinically meaningful concentrations of activated (unmasked) XTX202 within tumors and that any unmasked cytokine of XTX202 that reaches the systemic circulation will be rapidly cleared with minimal systemic AEs.

We then used syngeneic mouse tumor models to evaluate the activity of XTX202 *in vivo*. In these mouse tumor models, we observed tumor-activated PD effects of XTX202 and robust monotherapy activity against established tumors. Importantly, these experiments were conducted with XTX202 and not mouse surrogates.

We examined established B16F10 melanoma tumors for PD evidence of XTX202 activity and compared the results to activity seen systemically. These data were compared to the non-masked control XTX200 and the vehicle-treated negative controls. Animals received 10 mg/kg of XTX202 or 0.36 mg/kg of XTX200, the non-masked control, on day zero and day three.

The presence of CD8+ effector T cells was used as a measure of immune activation. The figure below depicts activity in B16F10 melanoma tumors on the left and in the spleen, a peripheral immune organ, on the right. We observed that both XTX202 and XTX200 induced an increase in CD8+ effector T cells in the tumor compared to vehicle control, while, in the spleen, expansion observed following XTX202 was limited compared to non-masked XTX200, which induced a significant expansion of splenic CD8+ effector T cells.

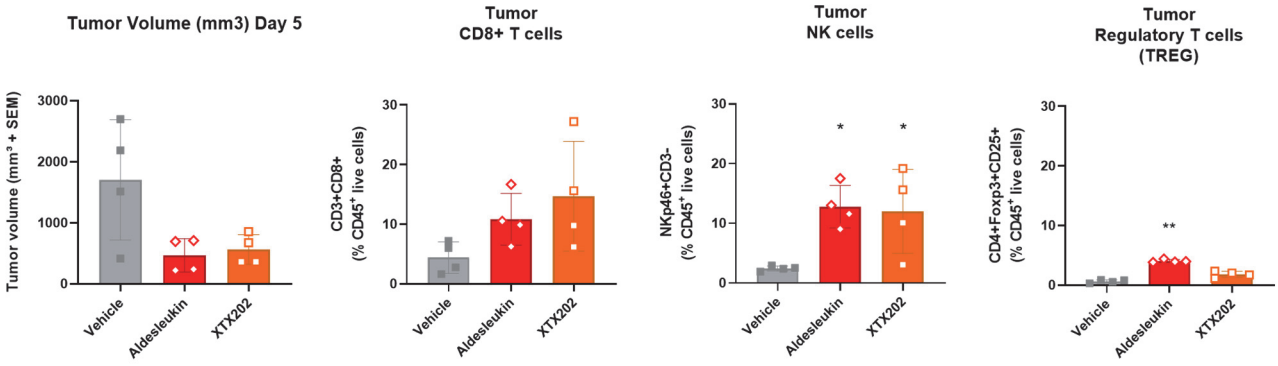
XTX202 Tumor Selectivity in B16F10 Tumor Mice



Female C57BL/6 mice were subcutaneously injected with a half million B16F10 cells. Animals were treated with 0.36mpk XTX200 or 10mpk XTX202 on days 0 and 3 when tumors reached 250mm³. Flow cytometry was performed on day 5. A one-way ANOVA Dunnett multiple comparison post-test was performed to determine the statistical significance of treatment vs vehicle. (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

In a separate experiment, we compared the effect of aldesleukin and XTX202 on tumor growth and the level of intra-tumoral CD8+ effector T cell, NK cell and TREG infiltration. MC38 tumor-bearing mice were treated with either vehicle, aldesleukin (3 mg/kg twice per day, or BID) or XTX202 (10 mg/kg once every five days, or Q5D) and tumor volumes, as well as intra-tumoral immune cell infiltration were assessed on day five post-treatment.

As illustrated in the figure below, XTX202 and aldesleukin treatment resulted in tumor growth inhibition, as well as increased CD8+ effector T cell and NK cell infiltration compared to vehicle. In contrast to aldesleukin, XTX202 treatment did not result in significantly increased intra-tumoral TREG frequencies compared to vehicle.

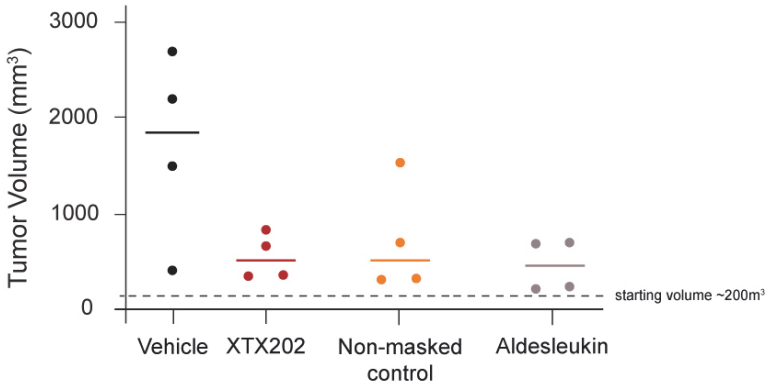


MC38 tumor-bearing mice were treated with either vehicle, aldesleukin (3 mg/kg BID) or XTX202 10mg/kg QDx5. Tumor volume was recorded at day 5 post first dose and tumor infiltrating immune cells were phenotyped and enumerated using flow cytometry. One-way ANOVA was performed to determine statistical significance. * p<0.05; ** p<0.001

In a separate experiment, we compared the ability of XTX202, XTX200 and aldesleukin to inhibit growth of established MC38 colon cancer tumors in mice. Prior experiments had demonstrated that 0.5 mg/kg of XTX200 dosed once every three days, or Q3D, and 3 mg/kg of aldesleukin BID for five days were the maximum tolerated doses, or MTDs, in mice

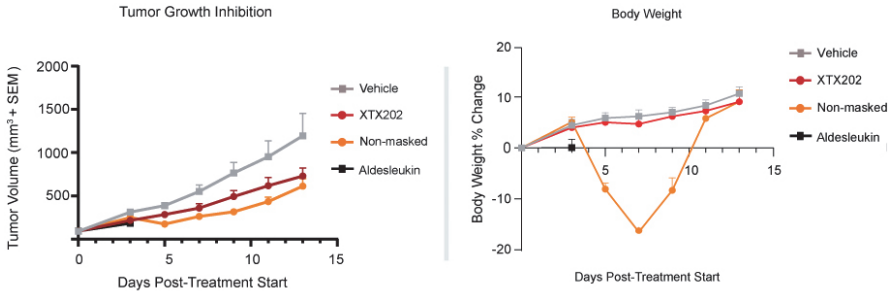
for these molecules. Previous experiments had also demonstrated that XTX202 was well-tolerated in mice at doses up to at least 25 mg/kg dosed Q3D, with reversible, mild decrease in body weight and no mortality, and no decrease in body weight at 10 mg/kg. In this study, on day zero, animals received 10 mg/kg of XTX202, a well-tolerated dose for this molecule, or XTX200 at an MTD of 0.5 mg/kg on day zero and day three, or aldesleukin at an MTD dose of 3 mg/kg BID on days zero through four. As shown in the below figure, on day 5 post-dose, a well-tolerated dose of XTX202 demonstrated comparable activity to aldesleukin or non-masked IL-2 at their MTDs.

XTX202 Tumor Growth Inhibition Was Comparable to Non-Masked Control XTX200 and Aldesleukin



We also conducted a preclinical study in a second syngeneic tumor model, using mice bearing established MB49 bladder cancer tumors. On day zero, mice received 2 mg/kg of XTX202, or 0.4 mg/kg of systemically active non-masked XTX200 every two days. Aldesleukin was given twice daily at 3 mg/kg for three days. As a result of the removal of one mouse from a study cohort due to mortality or unacceptable body weight loss, the tumor progression curve for that cohort has been censored. As shown in the left panel in the figure below, a well-tolerated dose of 2 mg/kg of XTX202 achieved similar activity to the non-masked IL-2 at its MTD of 0.4 mg/kg. As shown in the right panel, XTX202 at 2 mg/kg had no observed effect on weight gain compared to animals that received vehicle control. By contrast, 0.4 mg/kg of the non-masked molecule led to significant weight loss. The dose of aldesleukin required to match XTX202 activity was not tolerated in this study and resulted in animal mortality by day five. The tumor growth inhibition observed with the 2 mg/kg dose of XTX202 was comparable to the activity of the non-masked engineered IL-2 surrogate at its MTD, but body weight loss and mortality were seen in the aldesleukin group and activity could not be determined effectively.

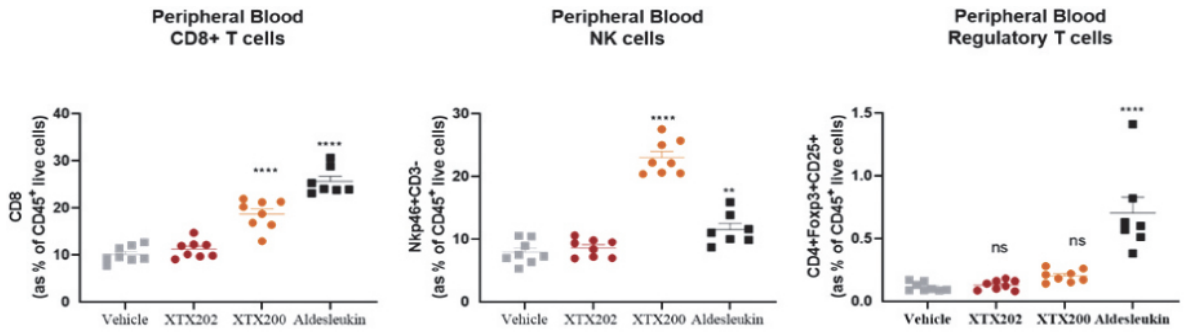
Effects of XTX202 on Tumor Growth Inhibition and Body Weight in MB49 Tumor Mice



TGI was measured on day 13 and a One-way ANOVA Dunnet's multiple comparison post-test was performed on day 13 to determine statistical significance of treatment vs vehicle (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

In the same MB49 tumor study, in animals in which effective tumor growth inhibition was observed, blood samples were collected on day five from all surviving animals. These samples were evaluated for changes in immune cell populations in the blood by fluorescent activated cell sorting. XTX202 did not cause an increase in circulating CD8+ effector T cells, NK cells or TREGs. In contrast, XTX200 caused an increase in circulating CD8+ and NK cells, but no effect on TREGs, and aldesleukin had variable but stimulatory effects on all three cell types.

XTX202 Did Not Affect Immune Cells in the Periphery

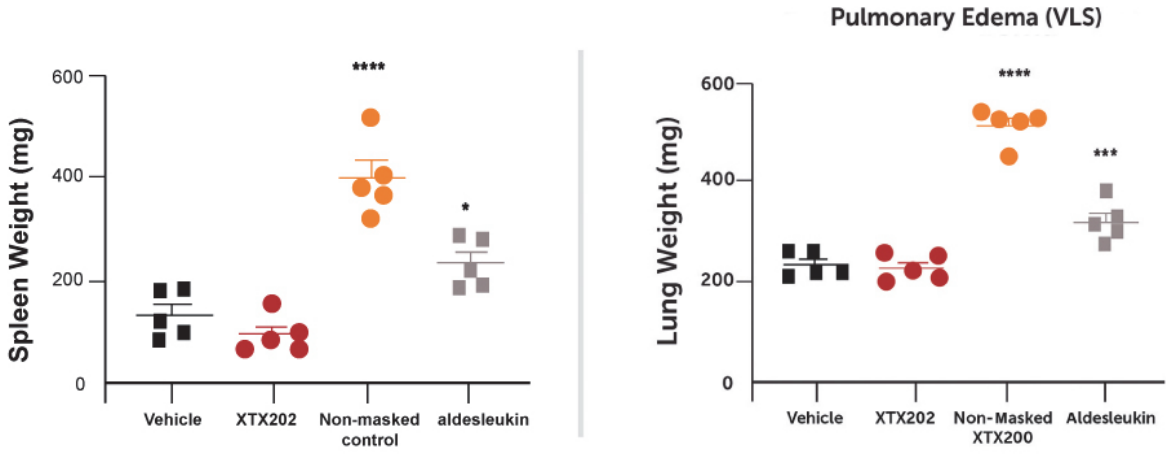


A One-way ANOVA Dunnet's multiple comparison post-test was performed to determine the statistical significance of treatment vs vehicle)*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001).

These preclinical data collectively support the hypothesis that the activity of XTX202 is limited to the tumor microenvironment. The lack of expansion of the CD8+ T cell, NK cell or Treg cell populations in the peripheral blood suggest that XTX202 achieved tumor growth inhibition while exhibiting no evidence of activity outside of the tumor microenvironment. By contrast, the non-masked molecule XTX200 and aldesleukin both showed significant increases in immune cell populations in the blood, demonstrating that these molecules are both active outside of the tumor microenvironment. This conclusion was further supported by measurements of animal health in the bladder cancer tumor model.

As shown in the figure below, we did not observe XTX202 to induce splenomegaly, while significant increases in spleen size were observed in animals treated with either XTX200 or aldesleukin. Similarly, XTX202 did not lead to VLS in treated mice as demonstrated by the lack of pulmonary edema, shown in the right panel. By contrast, XTX200 or aldesleukin administration resulted in vascular leak and pulmonary edema.

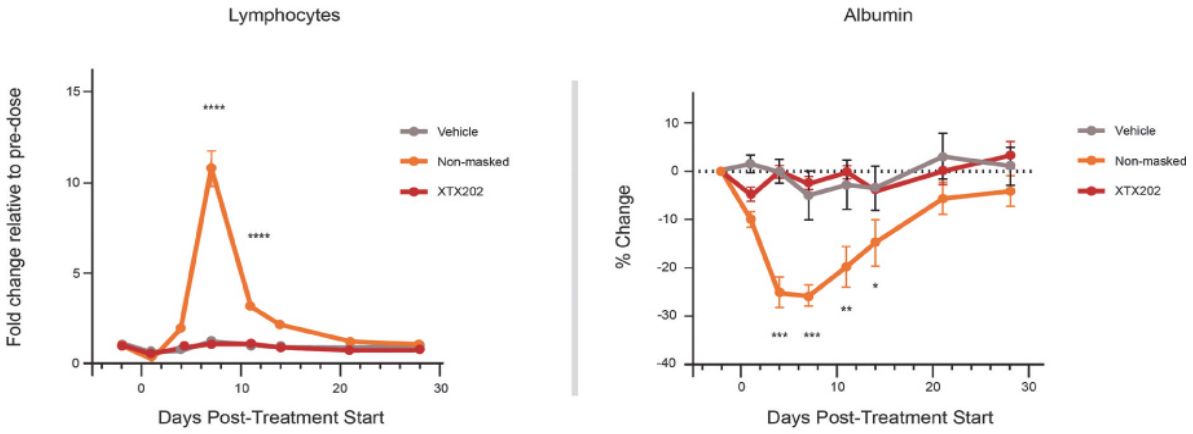
Splenomegaly and Pulmonary Edema Observed in Mice with Aldesleukin and Non-Masked XTX200, But Not with XTX202



A One-way ANOVA Dunnet's multiple comparison post-test was performed to determine the statistical significance of treatment vs vehicle (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

Tolerability of XTX202 and XTX200 was also evaluated in NHP studies. All animals were administered a single IV infusion of either XTX200 at 0.73 mg/kg or a masked analog of XTX202 at 1.0 mg/kg. Peripheral lymphocyte counts and serum albumin levels were monitored for four weeks post-administration. The data show that at a molar equivalent dose, the masked molecule does not result in lymphocytosis or hypoalbunemia that is induced by the unmasked version of the same non-alpha molecule (XTX200).

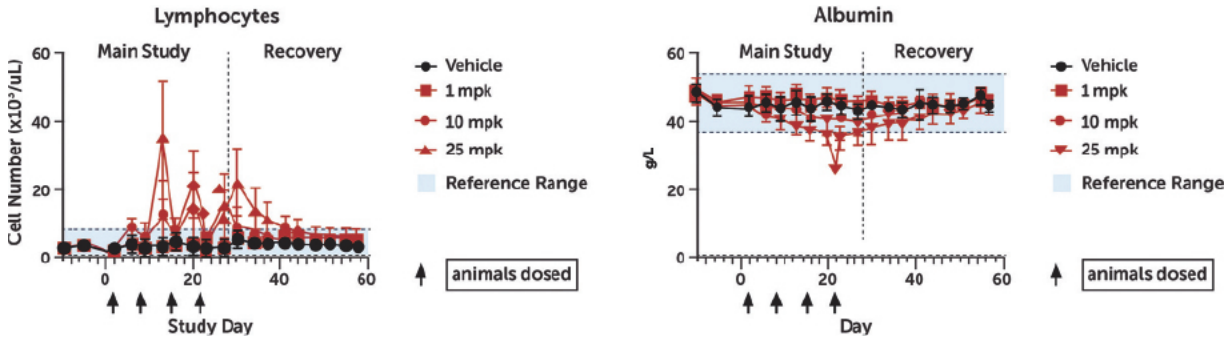
XTX202 Overcame Toxicity of Non-Masked XTX200 in NHPs



NHPs administered a single intravenous infusion: non-masked control at 0.73 mg/kg and a masked analog of XTX202 at equimolar dose of 1.0 mg/kg. A repeated measurement two-way ANOVA with Bonferroni's multiple comparison correction was performed to determine the statistical significance of treatment versus vehicle (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

XTX202 was evaluated in a repeat-dose toxicology study in NHPs in compliance with FDA's good laboratory practices, or GLPs. The study evaluated vehicle and 1, 10 and 25 mg/kg doses of XTX202 given once weekly intravenously. As shown in the figure below, we observed dose dependent lymphocyte expansion following administration of XTX202, with the 1 mg/kg group showing no systemic expansion. These results were further supported by analysis of circulating albumin. A decrease in serum albumin levels is an indication of VLS. Serum albumin remained within the normal range for the 1 mg/kg and 10 mg/kg dosing groups, indicating no systematic expansion occurred and demonstrating minimal or no systemic toxicity for XTX202 in those dosing groups. The results from this repeat-dose GLP toxicology study in NHPs demonstrated that XTX202 was well-tolerated with the highest non-severely toxic dose, or HNSTD, equal to 10 mg/kg when administered once per week for four weeks.

XTX202 Toxicology in a GLP NHP Study Demonstrated Favorable Tolerability



The circulating half-life and PK properties of masked XTX202 and non-masked control cytokine were evaluated in a preliminary NHP study. Drug levels were measured with a custom enzyme-linked immunosorbent assay following a single IV infusion of 1 mg/kg of XTX202 or the molar equivalent of XTX200 at 0.7 mg/kg. PK parameters were calculated using a non-compartmental analysis. As shown in the table below, XTX202 exhibited a half-life of 5.3 days, whereas the half-life of the non-masked XTX200 was shorter at 1 day. The half-life extension moiety and the decrease in target-mediated disposition due to masking of IL-2 result in the longer half-life of XTX202. These data support starting with a dosing schedule of intravenous administration once every three weeks, or Q3W.

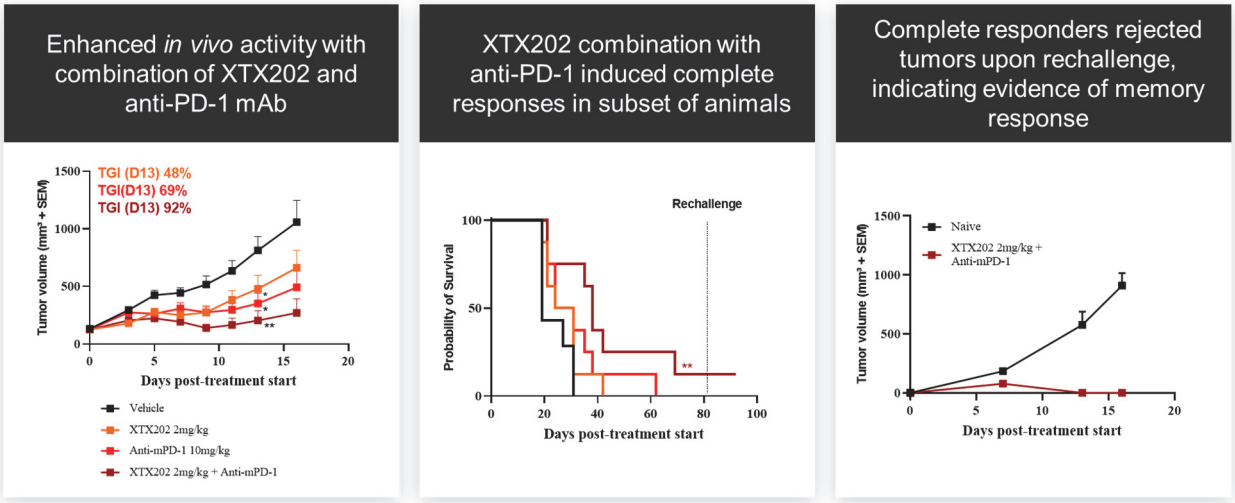
Measured PK Parameters in Single Dose NHP Study

	Half Life (Days)	Cmax (ug/mL)	AUCinf (hr*ug/mL)
XTX202 (masked at 1 mg/kg)	5.3	28.7	1,270
XTX200 (unmasked at 0.73 mg/kg)	1.0	16.7	423

Based on these data, we believe that circulating levels of masked XTX202 can be achieved with clinically meaningful concentrations of activated (unmasked) XTX202 within tumors and that any unmasked cytokine of XTX202 that reaches systemic circulation will be rapidly cleared with no systemic AEs.

We believe that our preclinical data support clinical development of XTX202 for the treatment of a range of cancer indications, both as a monotherapy and in combination with other agents. In head-to-head preclinical tumor model studies, XTX202 achieved activity with 2-10 mg/kg dosed Q3D comparable to aldesleukin at 3 mg/kg dosed BID. XTX202 was well-tolerated up to 10 mg/kg repeated administration over four weeks in NHPs, whereas the published MTD for aldesleukin in NHPs is 25 ug/kg daily for 28 days. Therefore, in our preclinical studies, XTX202 demonstrated a calculated improvement in overall therapeutic index compared to aldesleukin. While there can be no assurances that these results will be replicated in clinical trials, we believe these preclinical data demonstrate XTX202 has the potential to deliver high concentrations of IL-2 selectively to the tumor while minimizing peripheral toxicity. We expect this to allow dose-escalation to achieve intra-tumor cytokine levels high enough to induce local T cell and NK cell activation, proliferation and anti-tumor cytotoxicity.

In addition to the monotherapy potential for XTX202, we believe the combination of XTX202 with additional agents, including anti-PD-1/PD-L1 agents that are widely used in a range of solid tumors, has the potential to ultimately lead to the widest utilization of XTX202 in cancer patients. Based on preclinical data, we believe XTX202 has the potential to provide enhanced anti-tumor activity when combined with an anti-PD-1/PD-L1. As shown in the figure below, in preclinical studies, XTX202 combined with an anti-PD-1/PD-L1 induced complete responses in a preclinical setting where neither XTX202 nor the anti-PD-1/PD-L1 were able to achieve complete responses as a monotherapy. In these preclinical studies, mice with complete responses rejected rechallenge with tumor, indicating evidence of the development of a memory response.



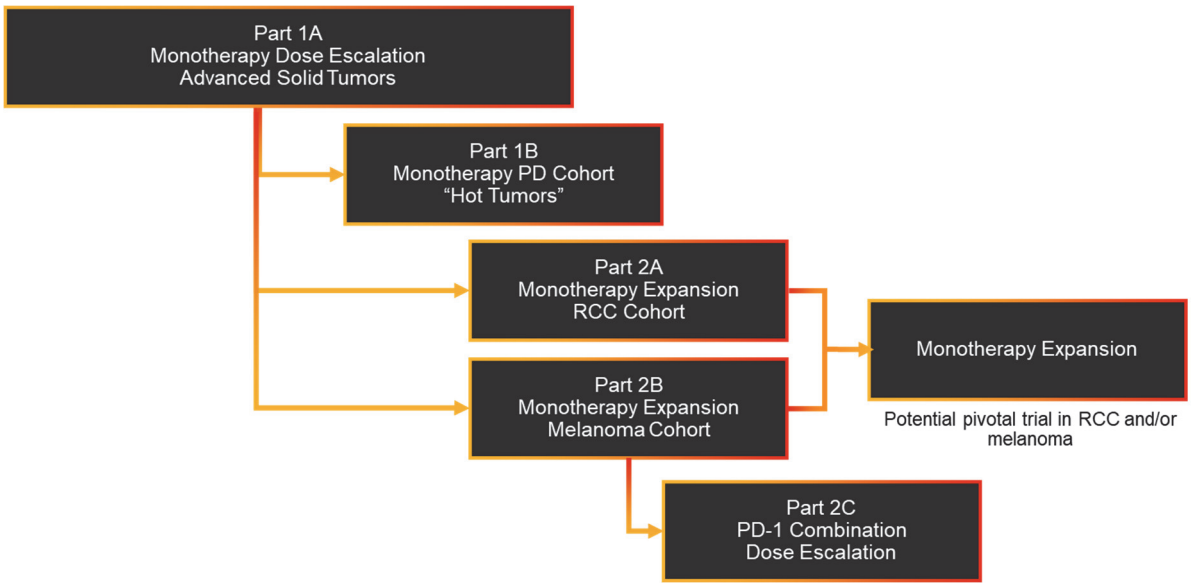
Anti-tumor activity of XTX202 as a single agent and in combination with anti-mPD-1 was evaluated in hFcRn Tg32 transgenic mice bearing the murine MB49 bladder carcinoma model. The combination of XTX202 with anti-mPD-1 further improved anti-tumor activity with TGI 92% on Day 13 (Data presented as mean ±SEM, two-way ANOVA followed by post hoc Dunnett's test, *P < 0.05; **P < 0.005). The treatment with XTX202 alone or in combination with anti-mPD-1 improved animal survival from 19 days to 27.5 and 38 days, respectively (Geham-Breslow-Wilcoxon test, **P < 0.01). A mouse with complete regression of MB49 tumor after combination therapy with XTX202 and anti-mPD-1 was resistant to tumor rechallenge with autologous MB49 tumor implanted on the opposite flank.

Clinical Development Plans for XTX202

We are currently evaluating XTX202 in monotherapy dose-escalation (Part 1A) in an ongoing Phase 1 clinical trial in patients with advanced solid tumors, and monotherapy dose expansion (Part 1B) is open for enrollment. The Phase 1 trial is a first-in-human, multi-center, open-label trial designed to evaluate the safety and tolerability of multiple ascending doses of XTX202 with the goal of establishing recommended Phase 2 dose, or RP2D, for XTX202 as a monotherapy in patients with advanced solid tumors. We plan to initiate patient enrollment in a Phase 2 clinical trial evaluating XTX202 as a monotherapy in patients with unresectable or metastatic melanoma and metastatic RCC in April 2023. The planned Phase 2 clinical trial for XTX202 is a multi-center, open-label trial designed to evaluate the safety and anti-tumor activity of XTX202 as a monotherapy in patients with unresectable or metastatic melanoma and metastatic RCC at the RP2D.

In addition, we plan to report preliminary anti-tumor activity, safety, PK and PD data from the Phase 1/2 clinical trial in the third quarter of 2023, which we anticipate will include approximately 15-20 patients across a range of solid tumors treated at the 1 mg/kg dose or higher across all cohorts in the Phase 1/2 clinical trial. Subject to these interim trial results and establishing initial clinical proof-of-concept for XTX202, we plan to complete the Phase 2 trial evaluating XTX202 as monotherapy in patients with RCC and melanoma with the goal of determining the potential to conduct monotherapy registration-enabling trials for XTX202. In parallel to the completion of the planned Phase 2 monotherapy trial, we plan to initiate a Phase 1/2 trial evaluating XTX202 in combination with an anti-PD-1/PD-L1 for the treatment of patients with NSCLC. Subject to the results from this combination study, we anticipate initiating registration-enabling clinical trials for XTX202 in combination with an anti-PD-1/PD-L1 in patients with NSCLC. We also plan to explore the potential for XTX202 in combination with other therapies, including combinations with XTX301, our tumor-activated IL-12, and potential collaborations with cell therapies or anti-cancer vaccines.

The figure below shows our Phase 1/2 trial design for XTX202 in RCC, melanoma and other indications to evaluate its activity as both a monotherapy and in combination with other agents.

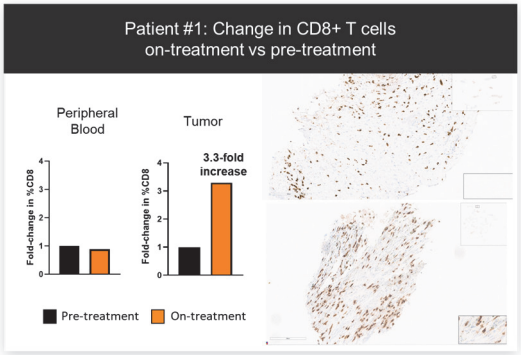


Phase 1 Clinical Trial for XTX202

We recently completed dosing patients at the 1 mg/kg dose level (dose level four) and are currently enrolling patients at the 1.4 mg/kg dose level (dose level five) in monotherapy dose-escalation (Part 1A) for our Phase 1 clinical trial. As of March 1, 2023, a total of 16 patients have been treated with XTX202 in the outpatient setting at five dose levels ranging from 0.27 mg/kg to 1.4 mg/kg Q3W in Part 1A for the Phase 1 clinical trial, and Part 1B is open for enrollment. No signs of VLS, including hypotension or decreases in albumin (an early sign of VLS) or hemodynamic compromise, have been

observed in patients to date. A maximum tolerated dose has not yet been determined, and enrollment in Part 1A and Part 1B of the clinical trial is ongoing.

In addition, we recently reported preliminary clinical intra-tumoral PD data for two patients treated with XTX202 who each had an optional on-treatment tumor biopsy and were the only two patients for whom a tumor biopsy analysis was available as of March 1, 2023. The first patient was a melanoma patient treated with XTX202 at the 0.38 mg/kg dose level, and the second patient was an RCC patient treated with XTX202 at the 0.53 mg/kg dose level. For each patient, as shown in the figures below, the tumor biopsy featured increased numbers of stromal TILs and increased frequency of CD8+ effector T cells among these TILs. Importantly, in each patient, at the time of the tumor biopsy, these changes occurred in the absence of peripheral changes to either CD8+ effector T cells, demonstrating preliminary evidence of tumor-selective activation.

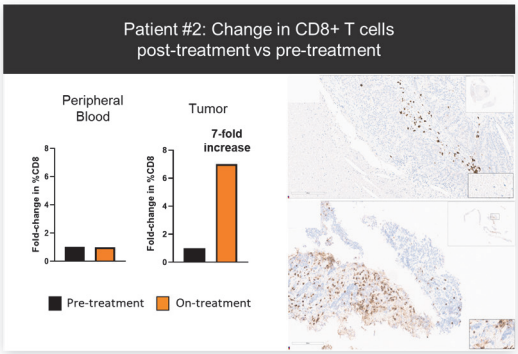


Patient #1 (Dose Level 2)

- 51-year-old male patient with melanoma
- Treated with XTX202 at 0.38 mg/kg Q3W in part 1A
- Prior treatment included IO and other systemic agents
- No signs or symptoms of VLS
- Biopsy obtained prior to treatment and prior to cycle 3 (6 weeks after cycle 1, day 1)

Patient #2 (Dose Level 3)

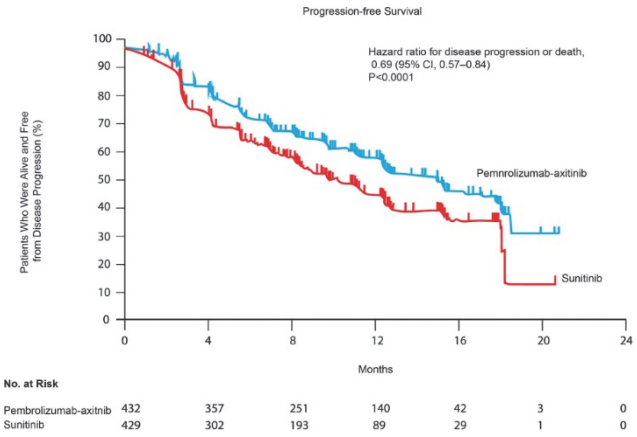
- 75-year-old male patient with RCC
- Treated with XTX202 at 0.53 mg/kg Q3W in part 1A
- Prior treatment included IO and other systemic agents
- No signs or symptoms of VLS
- Biopsy obtained prior to treatment and on cycle 2 day 20 (5 weeks after cycle 1, day 1)



Renal Cell Carcinoma (RCC) Overview

RCC accounts for 2% of global cancer diagnoses and deaths annually, and the global incidence is increasing. Most cases of RCC are discovered incidentally on imaging, and approximately one-third of cases are advanced or metastatic at the time of diagnosis. Survival is highly dependent on the stage at diagnosis, with metastatic disease having a five-year survival rate of only 15%. RCC is the ninth most common cancer in the United States, with approximately 79,000 estimated new cases in 2022 and approximately 13,920 deaths in 2022. The landscape of therapeutic options has rapidly evolved such that the treatment goal, even in the metastatic setting, is to cure patients or ensure their long-term survival. Systemic frontline therapy options now include combinations of checkpoint inhibitors and TKIs such as pembrolizumab and axitinib, nivolumab and ipilimumab, and avelumab and axitinib. Despite these recent approvals, there remains a pressing need to identify new therapeutic targets and effective treatments since the substantial majority of patients continue to experience relapses and progression and ultimately succumb to their cancer. As a result, cures are not commonly achieved, as in the example of pembrolizumab combined with vascular endothelial growth factor receptor-targeted TKI. As shown in the figure below, most patients with metastatic RCC will eventually relapse even after treatment with sunitinib or pembrolizumab and axitinib as the median time to progression-free survival, or PFS, is 11.1 months and 15.1 months, respectively.

Pembrolizumab+Axitinib Improved Overall Survival in Metastatic RCC, but Most Patients Still Relapsed Within 18 Months



In contrast to the TKI and anti-PD-1/PD-L1 combination shown above, IL-2-directed therapy offers the opportunity for durable responses and cures, as was seen in the historical aldesleukin treatment data. Only 15% of RCC patients treated with high-dose IL-2 obtained an objective response but approximately half of these, or 7% of all patients treated, achieved a CR. The unique feature of high-dose IL-2 is that approximately 90% of patients with RCC who achieved a CR remained permanently disease-free and off-treatment.

Assuming a successful Phase 1 dose escalation trial and identification of a RP2D, we plan to pursue a rapid Phase 2 proof-of-concept clinical trial in RCC, an indication in which recombinant IL-2 produces positive clinical responses, but in which its use is limited due to toxicity. We believe XTX202's characteristics can overcome these limitations and address the unmet need in RCC.

Treatment of Metastatic Melanoma with IL-2 Agents

In clinical trials evaluating recombinant IL-2 for the treatment of metastatic melanoma, recombinant IL-2 produced an ORR of 16% and produced CRs and functional cures in 6% of patients. However, use of recombinant IL-2 has been hampered by dose-limiting toxicities.

While treatments that target PD-1 and CTLA-4 have grown to dominate the metastatic melanoma treatment landscape, many patients do not respond, and relapses are common, with a five-year survival rate of around 50% in metastatic melanoma. We believe that a safe and effective form of IL-2 may improve initial response rates and clinical outcomes when added to checkpoint inhibitor therapy and may maintain responses in patients with melanoma who have relapsed from checkpoint inhibitor treatment. Importantly, high-dose IL-2 has shown a response rate, including CRs in patients with melanoma despite those patients having progressed on prior treatment with an anti-PD-1/PD-L1 showing the potential for IL-2 mechanism of action-based efficacy in patients who have previously been treated with an anti-PD-1/PD-L1.

Similar to our development plan for RCC, assuming a successful Phase 1 dose escalation trial, we plan to rapidly pursue a Phase 2 proof-of-concept clinical trial in melanoma, where recombinant IL-2 has demonstrated clinical responses but has been historically limited due to toxicity. Our clinical development plan includes the evaluation of patients with melanoma who have previously been treated with an anti-PD-1/PD-L1 to demonstrate clinical proof-of-concept.

Potential Future Indications

Beyond RCC and melanoma, we intend to explore XTX202 in additional solid tumor indications for which there is a significant unmet medical need, and for which IL-2 has previously demonstrated utility. These indications may include NSCLC, head and neck squamous cell cancer, or HNSCC, bladder cancer and ovarian cancer.

Aldesleukin has been studied in a broad range of tumor types. Dose-limiting toxicities have prevented most patients with cancer from receiving the high doses necessary for systemic efficacy. Multiple clinical trials have evaluated IL-2 where localized administration is possible. In these trials, IL-2 has induced objective responses in patients with ovarian cancer when administered in the peritoneum, in patients with bladder cancer when administered directly into the bladder and in patients with NSCLC and mesothelioma when administered into the pleural cavity. In patients with resectable HNSCC, perioperative administration of IL-2 into the lymph nodes near the tumor resulted in increased survival in a randomized trial. These data provide evidence that multiple tumor types are likely sensitive to IL-2 if high levels of localized exposure can be obtained.

In addition, we believe the novel design of XTX202 and preclinical and clinical data observed to date support the potential for XTX202 as a treatment in combination with other agents where tumor-activation may be required in order to combine with IL-2, including: monoclonal antibodies, other pro-inflammatory cytokines such as IL-12 and IL-18, cell therapies such as CAR-T and CAR-NK, and cancer vaccines.

XTX301, Our Clinical-Stage, Tumor-Activated IL-12 Product Candidate

XTX301 is an investigational tumor-activated, engineered IL-12 molecule designed to potently stimulate anti-tumor immunity and reprogram the tumor microenvironment of poorly immunogenic "cold" tumors towards an inflamed, or "hot," state. In November 2022, we announced clearance of our IND by the FDA for XTX301 for evaluation in patients with advanced solid tumors. We recently opened clinical trial sites and are actively screening patients for enrollment at a starting dose of 5.0 μg/kg (0.005 mg/kg) in monotherapy dose-escalation for our Phase 1 clinical trial evaluating the safety and tolerability of XTX301 in patients with advanced solid tumors. For more information, please see the section entitled "—Clinical Development Plans for XTX301" below.

Background on IL-12

IL-12 is a potent, pro-inflammatory cytokine produced by antigen-presenting cells such as dendritic cells, macrophages and B cells. IL-12 has two subunits, p35 and p40, that together form a heterodimer protein. IL-12 is a key cytokine in the body's response to pathogen infection, sending a signal to T cells, among others. IL-12 interacts with diverse immune cells, including CD4+ T cells, CD8+ effector T cells, NK cells, monocytes and macrophages. IL-12's broad range of pro-inflammatory functions suggests that it could potentially be highly potent in controlling anti-cancer immunity. IL-12 has been shown in preclinical studies to induce robust anti-tumor effects against many types of malignancies and it has been tested against multiple human cancers in clinical trials. Recombinant human IL-12 has been evaluated in clinical trials, and anti-tumor efficacy was observed in a small number of patients across a range of tumor types.

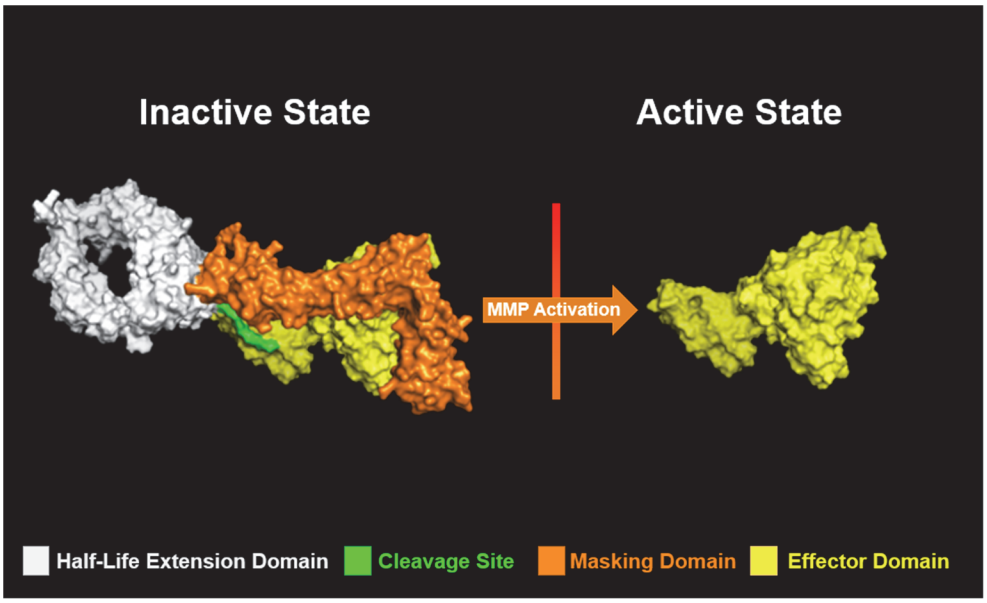
Unfortunately, systemic IL-12 therapy has historically caused severe AEs in patients with cancer. Life-threatening liver damage, called hepatotoxicity, was identified during the early development of previous IL-12 therapies, which severely limited the dose of IL-12 that could be administered, and further trials to evaluate efficacy were therefore conducted at sub-optimal doses due to the toxicity. In an early Phase 2 trial of recombinant IL-12, the MTD of 0.5 μg/kg per day caused severe side effects in 70% of patients, or 12 of 17 patients, of whom two died from gastrointestinal bleeding and multi-organ failure, respectively. The severe toxicities indicated that recombinant IL-12 could not be used systemically due to rapid increases in the cytokines IFN-γ, TNF-α and IL-6 that caused a cytokine storm syndrome characterized by systemic inflammation, multi-organ dysfunction and immune cytopenias. Efforts to overcome these systemic liabilities include alternate drug delivery approaches such as intra-tumoral administration of IL-12 encoding DNA vaccines or administration of oncolytic viruses expressing IL-12. Despite activity in individual lesions, cancer is a systemic disease that cannot be cured with local therapy once it has reached an advanced stage. Therefore, to unleash the potential for IL-12 in the majority of patients with advanced or metastatic cancer, an IL-12 that can be administered systemically but act locally at the tumor site is needed.

The failure of systemic IL-12 to induce meaningful anti-tumor efficacy is generally attributed to tolerability, which limits the dose and, as a result, the ability to reach therapeutic concentrations within the tumor microenvironment. Therefore, maximizing the amount of IL-12 that reaches the tumor, while minimizing exposure of non-tumor tissue, may be critical for a safe and effective anti-tumor response. Tumor-selective activation is therefore a desirable therapeutic profile.

Our Solution: XTX301, a Tumor-Activated IL-12

Our goal for our IL-12 program is to create a tumor-activated, extended half-life IL-12 therapeutic with minimal peripheral effects. We are using our GPS platform and proprietary approach to achieve systemic delivery of tumor-activated IL-12, which we believe would have potential as a monotherapy and in combination with other therapies.

The design of our masked IL-12 cytokine molecule is closely related to that of our masked IL-2 cytokine molecule, which illustrates the flexibility and robustness of our cytokine engineering approach. The masking domain is designed to prevent binding to the cell-surface IL-12 receptor, unless the linker containing the protease site is cleaved by proteases preferentially active in the tumor microenvironment. The half-life extension domain is designed to overcome the short circulating half-life of the native cytokine and the overall molecule is designed to enhance the efficiency of manufacturing.



Overview of preclinical studies and data

We have undertaken extensive preclinical studies that demonstrate the ability of XTX301 to induce potent anti-tumor activity and PD changes consistent with known IL-12 biology. Importantly, these effects on the tumor were observed without inducing concomitant systemic toxicity, which provides evidence that the masking design is performing as intended in preclinical studies. In murine preclinical models, we used a murine surrogate for XTX301, which we refer to as mXTX301, which included mouse sequences for IL-12 and the masking domain in place of the human sequences present in XTX301, since human IL-12 does not activate mouse IL-12 receptors. mXTX301 is architecturally analogous to XTX301 and shares the same half-life extension domain and protease linker as XTX301.

Collectively, our preclinical data showed that:

- XTX301 demonstrated minimal signaling through the IL-12 receptor when masked, and MMP activation of XTX301 restored potent IL-12 signaling in *in vitro* assays, illustrating the tight, protease-dependent control of IL-12 activity enabled by XTX301;

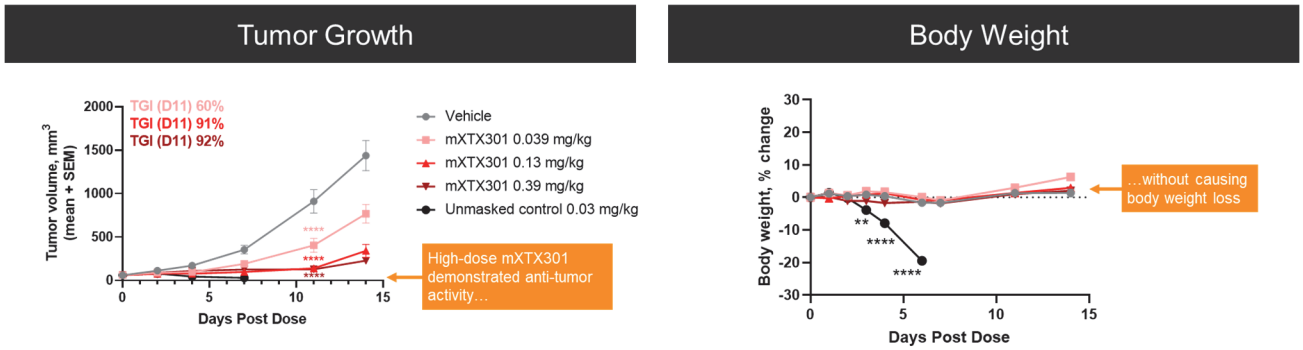
- mXTX301 treatment induced potent anti-tumor activity in response to single dose administration in multiple tumor models without inducing significant body weight loss and toxicity;

- mXTX301 treatment resulted in increased infiltration of CD8+ effector T cells into tumors and induced broad pro-inflammatory gene expression changes in tumors consistent with IL-12 biology and its ability to reprogram the tumor microenvironment towards a more immune-permissive state; and

- XTX301 was tolerated in NHPs at doses up to 2 mg/kg once weekly for four doses, or QWx4, and demonstrated a circulating half-life of four days.

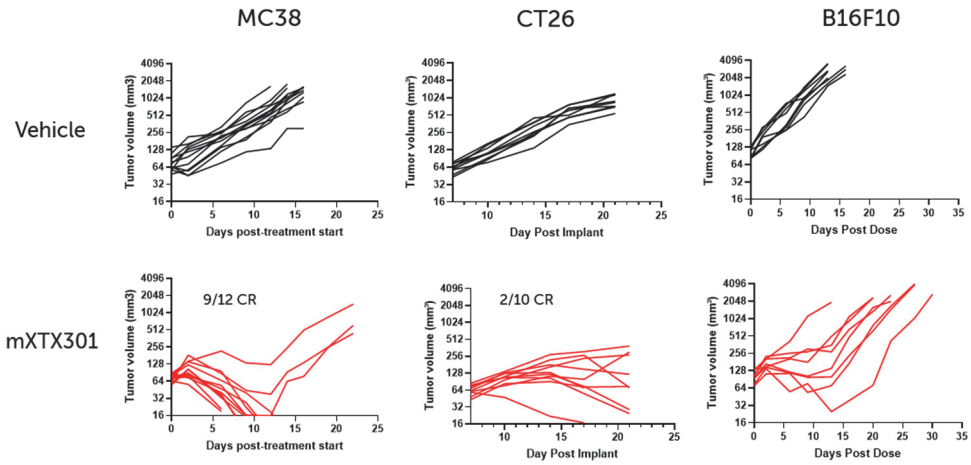
In preclinical models with mXTX301, tumor growth inhibition was observed in melanoma and bladder cancer models without AEs. Mice bearing established tumors received a single dose of mXTX301 at doses of 0.039 mg/kg, 0.13 mg/kg or 0.39 mg/kg or received 0.038 mg/kg of the non-masked mouse IL-12 cytokine, and tumor growth was measured over time.

As shown in the figure below, mXTX301 demonstrated anti-tumor activity in all doses tested, including complete regressions at the 0.13 mg/kg and 0.39 mg/kg dose levels in a subset of the mice dosed. While the non-masked mouse IL-12 cytokine also induced complete regressions, severe weight loss and mortality were observed, as compared to a lack of toxicity observed in all of the mice treated with mXTX301 across dose levels.



MC38 model: s.c. 0.5x106 cells; single IV dose of mXTX301 and mXTX302 on Day 0. Tumor growth data shown as mean±SEM. Tumor volume data was assessed by a two-way ANOVA followed by Bonferroni post hoc test on Day 11 compared to vehicle treated animals. ****p<0.0001 for all mXTX301 treatment groups. Body weight data are shown as mean ±SEM. A two-way ANOVA followed by Bonferroni post hoc test compared to vehicle treated animals was performed **p<0.005, ****p<0.0001.

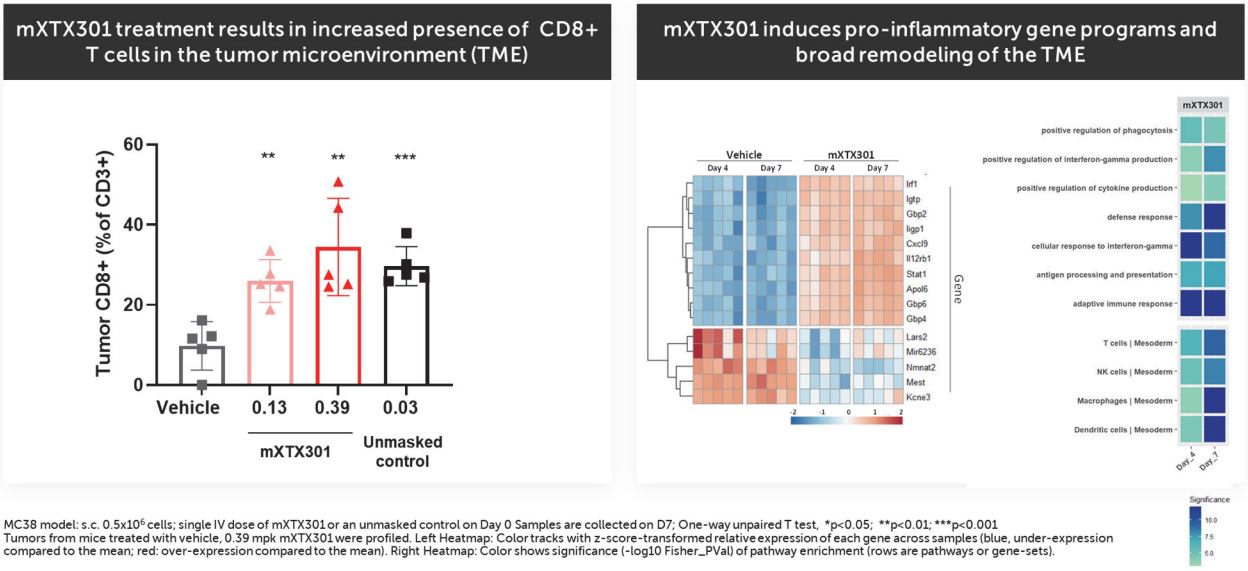
Additional experiments confirmed the anti-tumor activity of mXTX301 across a range of mouse models including MC38, CT26 and B16F10. As shown in the figure below, a single dose of mXTX301 treatment resulted in marked anti-tumor activity in all models, including complete regressions in a subset of animals with MC38 or CT26 tumors and transient regressions in a subset of mice with B16F10 tumors, which feature a "cold" non-inflamed tumor microenvironment.



Individual tumor volumes for MC38, CT26 or B16F10 tumor bearing animals treated with vehicle or a single dose of mXTX301 are shown over time. MC38 treated at 1.3 mg/kg, CT26 at 1.0 mg/kg and B16F10 at 3 mg/kg.

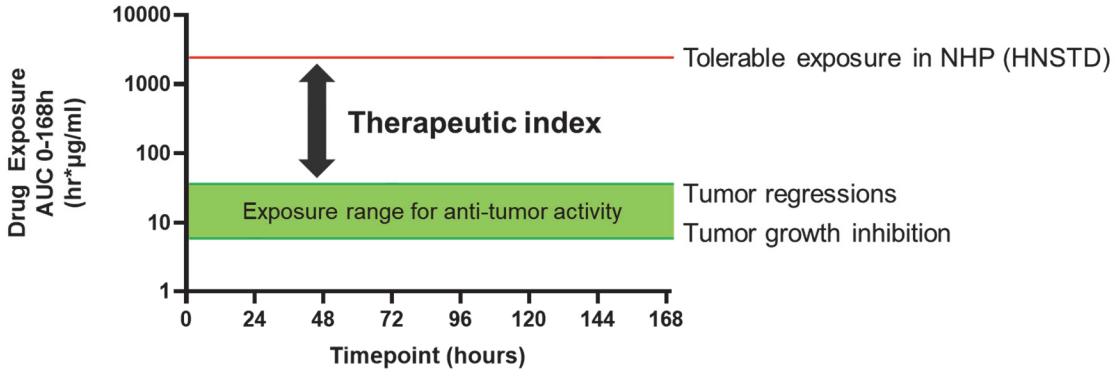
To gain deeper insight into the mechanism-of-action of XTX301, we conducted a series of experiments focused on measuring the effect of mXTX301 treatment on the tumor microenvironment in the MC38 model. The results of these experiments are summarized in the figure below.

Consistent with known IL-12 biology, mXTX301 treatment resulted in increased infiltration of CD8+ effector T cells into tumors. Additionally, mXTX301 induced robust gene expression changes indicative of broad immune activation in tumors including changes tied to infiltration of diverse immune cell subtypes, interferon gamma signaling and enhancement of antigen presentation.



MC38 model: s.c. 0.5x10^6 cells; single IV dose of mXTX301 or an unmasked control on Day 0 Samples are collected on D7; One-way unpaired T test, *p<0.05; **p<0.01; ***p<0.001
Tumors from mice treated with vehicle, 0.39 mpk mXTX301 were profiled. Left Heatmap: Color tracks with z-score-transformed relative expression of each gene across samples (blue, under-expression compared to the mean; red: over-expression compared to the mean). Right Heatmap: Color shows significance (-log10 Fisher_PVal) of pathway enrichment (rows are pathways or gene-sets).

In addition, preclinical data for XTX301 support the potential to achieve a broad therapeutic index. As shown in the figure below, in preclinical studies, mXTX301 induced tumor regressions in a murine model following a single dose of mXTX301 at 0.13 mg/kg, and XTX301 was tolerated at doses up to 2.0 mg/kg dosed once every week, or Q1W, four times in NHPs.



Compound	Assessment	Dose (mg/kg)	$AUC_{0\text{-}168}$ (hr*µg/mL)	Estimated Therapeutic Index (AUC_{Safety} / $AUC_{Activity}$)
mXTX301 (murine)	**Anti-tumor activity** (Tumor regressions)	0.13	37.8	**67**
XTX301 (human)	**Safety** (NHP)	2.0	2540	

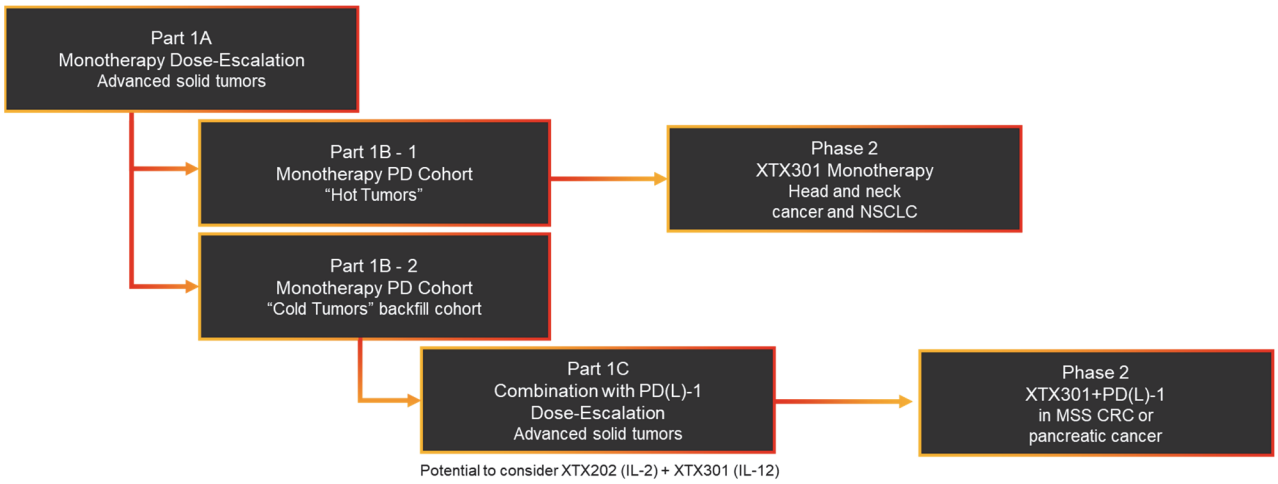
Measured PK Parameters in Single Dose NHP Study

	Half Life (Days)	Cmax (ug/mL)	AUCinf (hr*ug/mL)
XTX301 (2.0 mg/kg)	4.1	36.6	2795

Clinical Development Plans for XTX301

In November 2022, we announced clearance of our IND by the FDA for XTX301 for evaluation in patients with advanced solid tumors. We recently opened clinical trial sites and are actively screening patients for enrollment at a starting dose of 5.0 µg/kg (0.005 mg/kg) in monotherapy dose-escalation for our Phase 1 clinical trial evaluating the safety and tolerability of XTX301 in patients with advanced solid tumors. We anticipate reporting preliminary safety data from the Phase 1 clinical trial into at least the third dose level in the fourth quarter of 2023. Our clinical development plan for XTX301 will focus initially on monotherapy dose-escalation in patients with solid tumors. Subject to the successful completion of monotherapy dose-escalation, we anticipate evaluating initial PD and anti-tumor activity data in cohorts of patients focused on tumor types that are sensitive to treatment with I-O agents and a separate cohort of patients with tumor types historically insensitive to treatment with I-O agents. Following an assessment of anti-tumor effect as a monotherapy in selected tumor types, we also plan to explore the combination potential of XTX301 with an anti-PD-1/PD-L1 and with XTX202, our tumor-activated IL-2 product candidate, prior to initiation of registration-enabling clinical trials. Subject to the successful completion of trials showing the ability to combine XTX301 with other I-O agents and immune activation in "cold" tumors, we would plan to explore potential registration-enabling trials in both "hot" tumors, such as head and neck cancer and NSCLC, and in "cold" tumors, such as MSS CRC and pancreatic cancer.

The figure below shows our planned Phase 1/2 trial design for XTX301 to enable multiple monotherapy and combination opportunities for expansion in both hot and cold solid tumors.



XTX101, Our Clinical-Stage, Fc-Enhanced Tumor-Activated Anti-CTLA-4 Product Candidate

XTX101 is an investigational Fc-enhanced, tumor-activated anti-CTLA-4 mAb designed to deplete regulatory T cells when activated (unmasked) in the tumor microenvironment and improve upon the therapeutic index of existing anti-CTLA-4 therapies. We are currently evaluating XTX101 in an ongoing Phase 1 clinical trial in patients with advanced solid tumors. For more information, please see the section entitled "—Clinical Development Plans for XTX101" below. As previously announced, we plan to continue to explore strategic opportunities to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

Background on CTLA-4

CTLA-4 is an immune checkpoint protein that is well-established as playing a central role in the development of tumors. The scientific insight that led to the early development of CTLA-4 therapeutics is attributable to investigators recognizing CTLA-4 as a protein on T cells that acts as a brake on T cell activation. By removing this brake, T cells were freed to attack cancer. This work led to the development and FDA approval of ipilimumab, a CTLA-4 mAb, for the treatment of unresectable or metastatic melanoma at a dose of 3 mg/kg in 2011 and in additional indications in subsequent years.

While anti-CTLA-4 therapies such as ipilimumab have demonstrated meaningful efficacy across a range of tumor types, autoimmune toxicities have significantly limited their use to date. Clinical trials have shown that 20% of ipilimumab-treated melanoma patients survive at least three years, and a subset survive for 10 years or longer. Ipilimumab remains one of the most impactful drugs for these patients; however, the number of patients who benefit from treatment with ipilimumab remains limited due to its toxicity. Investigation of dose-response in two third-party clinical trials of melanoma patients showed that higher doses of ipilimumab are likely to increase the proportion of patients who benefit; however, the increased dose also resulted in an unacceptable toxicity profile for most patients. In a Phase 2 trial of ipilimumab conducted by Bristol-Myers Squibb Company, a dose range of 0.3 mg/kg to 10 mg/kg was tested and efficacy was measured both by response rate and by clinical outcome. Both the response rate and median overall survival, or mOS, were higher at 10 mg/kg than at 3 mg/kg, with the 0.3 mg/kg dose determined as being ineffective. The rate of severe AEs was 25% at the 10 mg/kg dose, 7% at the 3 mg/kg dose and 0% at the ineffective dose of 0.3 mg/kg. Similarly, as shown in the table below, in a Phase 3 trial conducted by Bristol-Myers Squibb Company, mOS was higher at the 10 mg/kg dose but resulted in unacceptable toxicity for most patients. Therefore, we believe that achieving a three-fold increase in therapeutic index would be transformational.

High-Dose Ipilimumab Improved Survival but Resulted in Unacceptable Toxicity

Dose (mg/kg)	mOS (mo)	Adverse Events: Gr 3/4 irAEs / disconts. (%)
3	**11.5**	**14 / 19**
10	**15.7**	**30 / 31**

Ipilimumab has shown preliminary evidence of promising anti-tumor activity in a range of tumor types outside of its currently approved indications, but successful additional approvals have been limited due to its toxicity. For example, ipilimumab has been observed to be more active when combined with the anti-PD-1/PD-L1 antibody nivolumab. However, the combination of ipilimumab and nivolumab has been shown to cause a greatly increased rate of immune-related toxicity when compared to treatment with either ipilimumab or nivolumab as a monotherapy. Clinical results from patients who express high-affinity FcγR polymorphisms have shown improved responses to ipilimumab, but efforts to improve the potency of the antibody have been limited by perceived toxicity risk. There remains a critical need to develop safe and effective forms of anti-CTLA-4 mAbs that can achieve efficacious doses within the tumor microenvironment.

Our Solution: XTX101, a Fc-Enhanced, Tumor-Activated Anti-CTLA-4

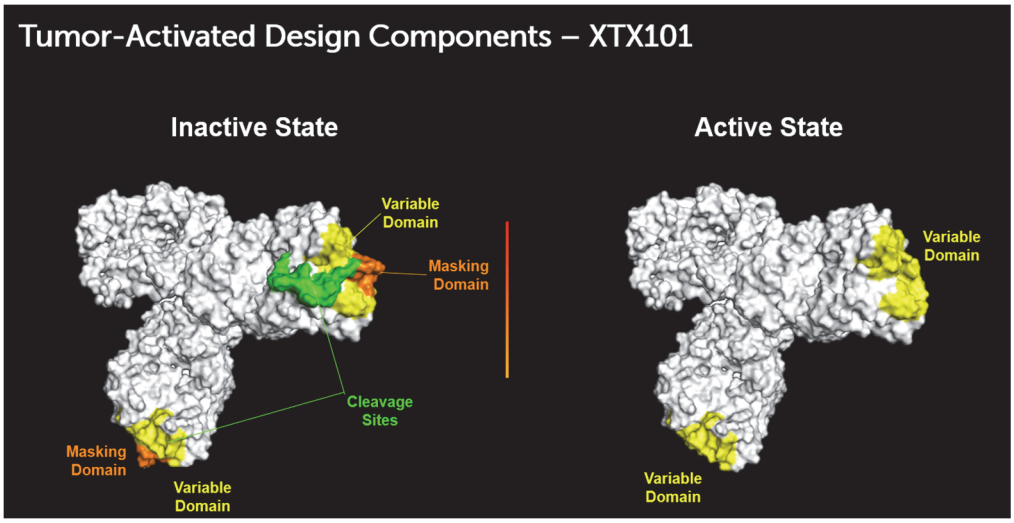
XTX101 is a clinical-stage, Fc-enhanced, tumor-activated anti-CTLA-4 mAb that is designed to improve upon the therapeutic index of existing anti-CTLA-4 therapies by overcoming potency and tolerability limitations. Our goal is to demonstrate an improved safety profile enabling higher anti-CTLA-4 exposure in the tumor that will result in increased efficacy. In preclinical studies, we have observed the following tolerability and activity profile of XTX101:

- improved *in vivo* potency and the intra-tumoral PD effects of XTX101 are consistent with the improved potency being a result of the higher affinity binding to the target CTLA-4 and enhanced IgG1-Fc effector function, which further improves checkpoint inhibition and enhances antibody-dependent cellular cytotoxicity to deplete immune-suppressive TREGs in the tumor microenvironment;

- reduced peripheral immune activity due to masking of the CDR sequences; and

- activation by protease-dependent release of the masks, which acts selectively in the tumor microenvironment and minimizes toxicity associated with systemic immune activation.

XTX101 is designed to enhance the desirable features of an anti-CTLA-4 antibody while mitigating the known limitations of anti-CTLA-4 antibodies due to toxicity. We expect this combination of features to result in an increased therapeutic index.



Overview of preclinical studies and data

We have examined XTX101 in several preclinical and IND-enabling studies that we believe have demonstrated the potential for XTX101 to have an enhanced activity and an improved tolerability profile compared to ipilimumab. As summarized below, we believe that these studies collectively provide preclinical proof-of-concept with an improved therapeutic index due to tumor microenvironment-dependent activation of XTX101 that, if replicated in clinical trials, could result in significant benefits to patients with a variety of different solid tumors.

- XTX101 showed tight control and full reliance on MMP activity for binding to CTLA-4 in an *in vitro* study using a sensitive surface plasmon residence, or SPR, assay.

- XTX101 was activated by human tumors in a study of 82 tumor biopsies across a variety of solid tumors that demonstrated 67% overall activation.

- XTX101 demonstrated activity similar to an ipilimumab analog in *in vivo* mouse models of bladder cancer tumor growth. XTX101 dosed at 0.3 mg/kg and 1.0 mg/kg resulted in 2/8 CRs and 5/8 CRs, respectively.

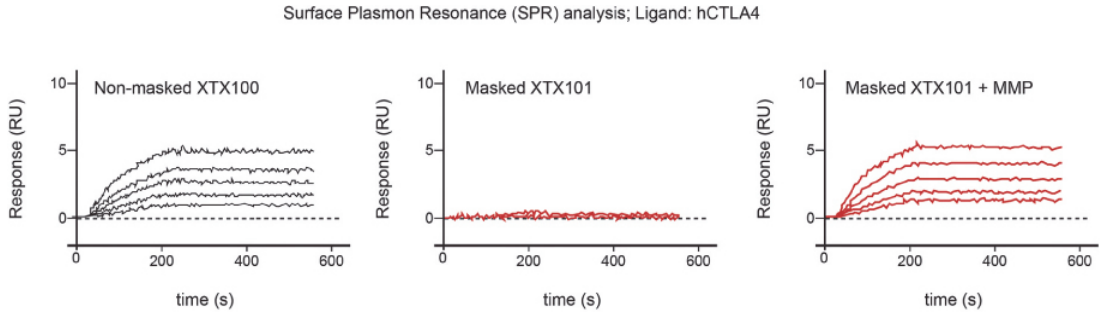
- In the same mouse study, we observed that XTX101 induced an increase in CD8+ effector T cells within the tumor and a decrease in TREGs in the tumor, without increasing CD4+ T cells in the blood. The ipilimumab analog had less activity than XTX101 in the tumor but did show an increase in CD4+ T cells in the blood.

- In a separate mouse study, the combination of XTX101 and an anti-PD-1/PD-L1 antibody showed robust tumor growth inhibition in excess of either drug as a monotherapy, with minimal systemic toxicity.

We observed the dependency of XTX101 on proteolytic cleavage to achieve binding using an SPR assay, which measures on-rate and off-rate of antibody binding to the target protein, allowing an accurate assessment of binding. The data demonstrate tight control and full reliance on MMP activity for binding of XTX101 to CTLA-4. The figure below shows protease-dependent activation of XTX101 *in vitro* using a biophysical assay. The left panel shows the binding of non-masked anti-CTLA-4 mAb, XTX100, to CTLA-4 coated on the SPR chip. Binding is indicated by a positive response

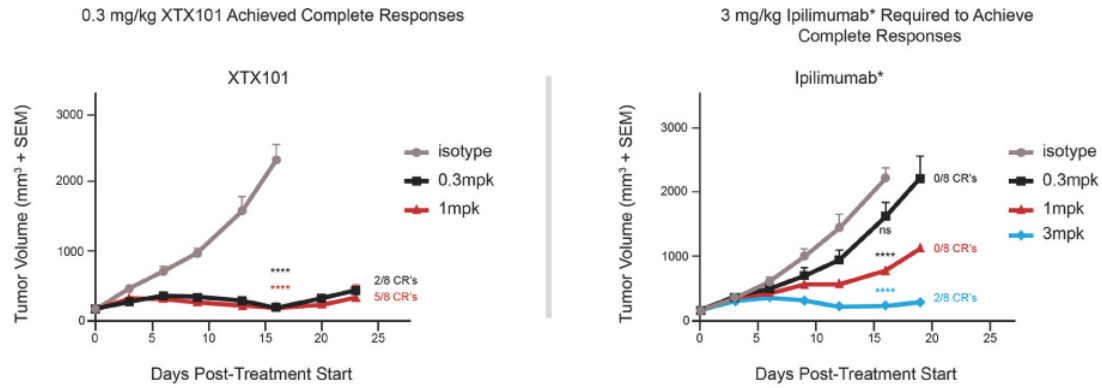
measured in resonance units, or RUs. The middle panel shows minimal binding of unmasked anti-CTLA-4 mAb, XTX101, under the same conditions. The right panels show that treatment of masked XTX101 with MMPs restores binding to CTLA-4 in the SPR assay.

After Proteolytic Activation, Full Binding was Restored to XTX101



In *in vivo* models of bladder cancer tumor growth, XTX101 showed activity superior to that of an ipilimumab analog. MB49 cells were inoculated subcutaneously into C57BL/6-huCTLA-4 mice. When tumors reached approximately 150 mm3, mice received a single intravenous, or IV, dose of each molecule at the doses indicated in the figure. These were 0.3 mg/kg or 1.0 mg/kg for XTX101 and 0.3 mg/kg, 1.0 mg/kg and 3.0 mg/kg for the ipilimumab analog, which we produced to conduct these studies. As shown in the figure below, we observed that XTX101 was more clinically active than the ipilimumab analog in the MB49 bladder cancer model. The left panel shows the effect of different doses of XTX101 on tumor growth, with two CRs achieved with a dose of 0.3 mg/kg and five CRs achieved with a dose of 1.0 mg/kg. The right panel shows the effect of different doses of the ipilimumab analog on tumor growth, with no CRs achieved with a dose of either 0.3 or 1.0 mg/kg. XTX101 exhibited superior tumor growth inhibition compared to the ipilimumab analog. A dose of 3 mg/kg of the ipilimumab analog was required to achieve similar activity and CR rate as XTX101 at 0.3 mg/kg, suggesting XTX101 has 10-fold higher potency than the ipilimumab analog.

Clinical Activity of XTX101 and Ipilimumab Analog in MB49 Tumor Mice



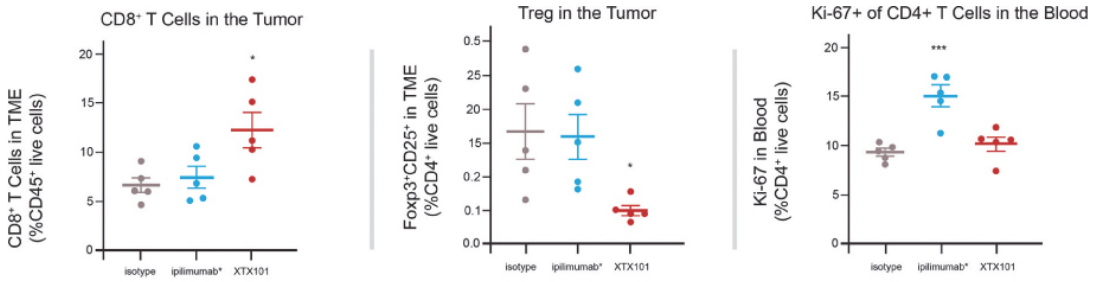
* Ipilimumab: ipilimumab analog that comprises a monoclonal antibody of identical amino acid sequence to ipilimumab that was produced at Xilio for research purposes

A Two-way ANOVA with Bonferonni's multiple comparisons post-test was performed to determine the statistical significance of treatment vs. isotype on day 16 (ns not significant; *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

Further, as shown in the below figure, we observed that XTX101 induced an increase in CD8+ effector T cells within the tumor, as shown in the left panel, and a decrease in TREGs in the tumor, as shown in the middle panel. We observed that XTX101 did not promote an increase in CD4+ T cells in the blood even at 3 mg/kg despite achieving complete responses at 0.3 mg/kg, suggesting tumor-activated activity of XTX101. We further observed that the ipilimumab analog promoted an increase in CD4+ T cells in the blood at the 3 mg/kg dose required for efficient tumor growth inhibition in the blood,

as shown in the right panel, demonstrating that the ipilimumab analog was active outside of the tumor microenvironment at doses required for activity.

XTX101 Demonstrated Tumor-Activated PD and Treg Depletion



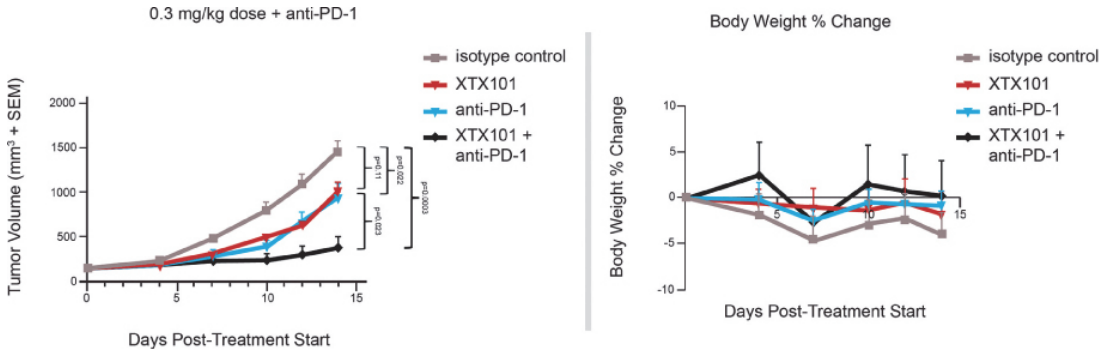
* ipilimumab analog that comprises a monoclonal antibody of identical amino acid sequence to ipilimumab that was produced at Xilio for research purposes

A two-way ANOVA with Dunnett's multiple comparisons post-test was performed to determine the statistical significance of treatment versus isotype control (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001).

The effect of the combination of XTX101 with anti-PD-1/PD-L1 antibody was evaluated in another preclinical study in which female C57BL/6-huCTLA-4 mice, were implanted subcutaneously with MC38 cells. When the tumors reached approximately 150 mm^3 on day zero, the mice were intravenously administered 10mg/kg isotype control antibody, 0.3 mg/kg of XTX101 or 10mg/kg anti-PD-1/PD-L1.

As shown in the figure and table below, XTX101 and the anti-PD(L)-1 antibody each showed limited activity as a monotherapy. However, the combination of XTX101 with the anti-PD(L)-1 antibody showed robust tumor growth inhibition of 82%, including two out of eight animals achieving a CR. Minimal toxicity was observed in animals treated with either monotherapy or the combination, suggesting that XTX101 can be effectively combined with an anti-PD-1/PD-L1 antibody without enhanced toxicity.

Single Dose Combination of XTX101 with anti-muPD-1 Enhanced Tumor Growth Inhibition with No Impact on Body Weight



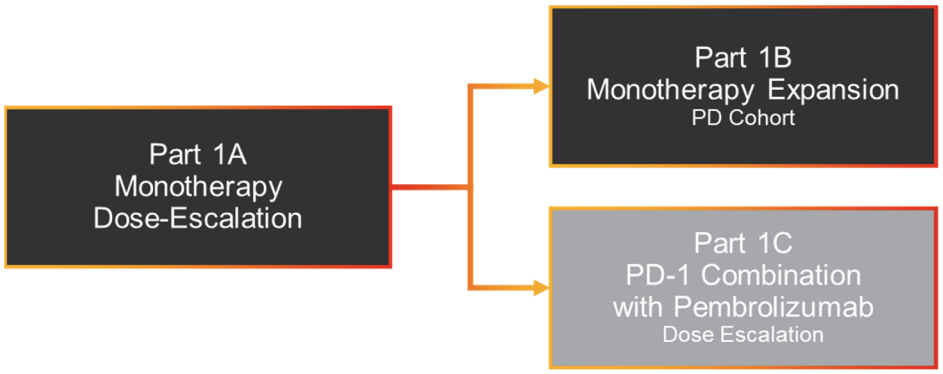
	Isotype Control	XTX101 0.3 mg/kg	anti-PD-1/PD-L1 10 mg/kg	XTX101 0.3 mg/kg + anti-PD-1/PD-L1
% TGI Day 14	N/A	34	40	82
P values	N/A	0.022	0.11	0.0003
Complete responses	0/8	0/8	0/8	2/8

In GLP toxicology studies completed in NHPs, XTX101 exhibited a highest non-severely toxic dose, or HNSTD, of 3 mg/kg, supporting the targeted clinical dose for XTX101 in patients of 1-3 mg/kg. In addition, the half-life for XTX101 was 92 to 208 hours in single dose studies in NHPs, supporting the potential for dosing once every three weeks.

Clinical Development Plans for XTX101

In September 2021, we initiated a first in-human, multi-center, open-label Phase 1 trial designed to evaluate the safety and tolerability of XTX101 for the treatment of adult patients with advanced solid tumors. As of March 1, 2023, 24 patients have been treated with XTX101 in the Phase 1 trial. Enrollment in monotherapy dose-escalation (Part 1A) of the Phase 1 trial has been completed, and enrollment in monotherapy dose-expansion (Part 1B) is ongoing. In addition, we have determined an RP2D of 150 mg Q6W. We anticipate reporting preliminary safety, PK, PD and anti-tumor activity data from the Phase 1 clinical trial in the second quarter of 2023. As previously announced, we plan to continue to explore strategic opportunities to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

The figure below shows our Phase 1 trial design for XTX101.



Future Discovery Opportunities Leveraging Our GPS Platform for Tumor-Activation and Tumor-Targeting

We have prioritized efforts to develop novel cytokines, checkpoint inhibitors and multi-functional molecules based on the therapeutic activity established in other clinical trials, while recognizing that their benefit has been historically hampered by issues of significant toxicity, poor bioavailability and, in the case of cytokines, a short half-life. By leveraging the insights and capabilities of our GPS platform, we aim to systematically create novel cytokines, checkpoint inhibitors and multi-functional molecules that overcome these challenges in order to safely localize their potent activity to the tumor microenvironment.

We believe our proprietary GPS platform has the potential to develop additional product candidates using a range of approaches to achieve tumor-selective activation and derive a clinically meaningful improvement in therapeutic index. We intend to further advance our tumor-activated therapeutic platform combining our masking approach with active, antibody-directed tumor targeting to create multi-functional, masked molecules designed to enable enhanced selectivity down to the cellular level and modulating multiple immune pathways synergistically. Preliminary data from preclinical studies indicates the promise of this approach, as the addition of a targeting domain to a tumor-activated masked cytokine has demonstrated superior tumor growth inhibition and tumor-specific PD activity compared to the same masked cytokine without the targeting. In addition, in these preclinical studies the masked targeted cytokine has demonstrated superior safety compared to a non-masked version of the same targeted cytokine.

We plan to evaluate the opportunity for better tolerated and more efficacious combination therapies, using product candidates from across our portfolio with other cancer therapies, to increase the potential for curative regimens in oncology. Beyond oncology, we also plan to apply our GPS platform to other disease areas in which the immune system is dysregulated, such as in autoimmune and inflammatory diseases.

Competition

We believe our novel and proprietary GPS platform and masking approach represent a meaningful competitive advantage in seeking to develop novel and highly effective treatments for cancer. However, the biotechnology and biopharmaceutical industries are characterized by rapid evolution of technologies and sharp competition and emphasis on intellectual

property. Any product candidates that we successfully develop and commercialize will have to compete with existing therapies and new therapies that may become available in the future. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions.

Some of our competitors, either independently or with strategic partners, have substantially greater financial, technical and human resources than we do. In addition, our competitors may be more successful than we are in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approval for treatments and achieving widespread market acceptance. Merger and acquisition activity in the biotechnology and biopharmaceutical industries may result in resources being concentrated among a smaller number of our competitors. These companies also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

In addition to competitors specifically targeting IL-2, IL-12, and anti-CTLA-4, we also face competition more broadly across the oncology market. The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy, biologic therapy, such as monoclonal and bispecific antibodies, immunotherapy, cell-based therapy and targeted therapy, or a combination of any such treatments. Beyond these treatments, we may also be subject to competition from additional modalities, including oncolytic viruses and cancer vaccines.

Our commercial opportunity could be substantially limited if our competitors develop and commercialize products that are more effective, safer, less toxic, more convenient, or less expensive than products we may develop. In geographies that are critical to our commercial success, competitors may also obtain regulatory approvals before us, resulting in our competitors building a strong market position in advance of the entry of our products. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of other drugs. The key competitive factors affecting the success of any products we may develop are likely to be their efficacy, safety, convenience, price and availability of reimbursement.

Cytokine Programs

With respect to our most advanced cytokine product candidate, XTX202, if approved, it may face competition from other IL-2 based cancer therapies. For example, Proleukin (aldesleukin), a synthetic protein very similar to IL-2, is approved and marketed for the treatment of metastatic RCC and melanoma. In addition, we are aware of several companies that have modified or low-dose IL-2 programs in development for the treatment of cancer, including Alkermes plc, Anaveon AG, Ascendis Pharma A/S, Asher Biotherapeutics, Inc., Aulos Bioscience, Inc., Bright Peak Therapeutics, Cue Biopharma, Inc., Cugene Inc., Egle Therapeutics SAS, GI Innovation, Iovance Biotherapeutics, Inc., Medicenna Therapeutics Corp., Medikine, Inc., Modulate Therapeutics, Inc., Neoleukin Therapeutics, Inc., Philogen S.p.A., Roche AG, Sanofi, Selecxine, Synthekine, Inc., Trutino Biosciences Inc., Werewolf Therapeutics, Inc., XOMA Corporation and Zydus Cadila.

With respect to XTX301, there are no approved IL-12 therapies currently on the market for the treatment of cancer; however, we are aware of several other companies that have modified IL-12 or intra-tumoral IL-12 delivery programs for the treatment of cancer in development, including Amunix Pharmaceuticals, Inc., AstraZeneca plc / Moderna, Inc., Cullinan Management Inc., Dragonfly Therapeutics, Inc., ImmunityBio, Inc., PDS Biotechnology Corporation, Philogen S.p.A., Sonnet BioTherapeutics, Werewolf Therapeutics, Inc., Xencor Inc. and Zymeworks Inc.

Anti-CTLA-4 Therapies

We are aware of a number of companies that are developing anti-CTLA-4 therapies as immunotherapies. With respect to XTX101, if approved, we may face competition from other anti-CTLA-4 based therapies. For example, Yervoy (ipilimumab), an anti-CTLA-4, is approved to treat melanoma, RCC, NSCLC and certain cancers of the large intestine. In

addition, we are aware that several companies have anti-CTLA-4 programs in development, including Adagene, Inc., Agenus Inc., AstraZeneca plc, BioAtla Inc., Bristol-Myers Squibb Inc., CytomX Therapeutics, Inc. and MacroGenics, Inc.

Intellectual Property

We strive to protect our proprietary technology, inventions, improvements, and platforms, including composition of matter for product candidates, methods of use and processes for their manufacture that we believe are important to our business, including by obtaining, maintaining, defending and enforcing patent and other intellectual property rights for the foregoing in the United States and in certain foreign jurisdictions. We also rely on trade secrets and confidentiality agreements to protect our confidential information and know-how and other aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success depends in part on our ability to:

- obtain, maintain, enforce and defend patent and other intellectual property rights for our commercially important technology, inventions and improvements;
- preserve the confidentiality of our trade secrets and other confidential information;
- obtain and maintain licenses to use and exploit intellectual property owned or controlled by third parties;
- operate without infringing, misappropriating or otherwise violating any valid and enforceable patents and other intellectual property rights of third parties; and
- defend against challenges and assertions by third parties challenging the validity or enforceability of our intellectual property rights, or our rights in our intellectual property, or asserting that the operation of our business infringes, misappropriates or otherwise violates their intellectual property rights.

Patent portfolio

As of February 15, 2023, we own, co-own or exclusively license 16 patent application families related to our business, including four pending Patent Cooperation Treaty, or PCT, patent applications, 15 pending U.S. non-provisional applications, two issued U.S. patents, three issued patents in Indonesia, Japan and South Korea and 144 pending foreign applications in Europe, Japan, China, Australia, Brazil, Canada, Eurasia, Hong Kong, Indonesia, Israel, India, South Korea, Mexico, Malaysia, New Zealand, the Philippines, Saudi Arabia, Singapore, South Africa and Taiwan, including five allowed patent applications. In addition, we own four U.S. provisional patent applications within the priority year. Our owned, co-owned or exclusively in-licensed patent applications cover various aspects of our programs and technology, including composition of matter and method of use as further described below. Any U.S. or foreign patents issued from national stage filings of our owned, co-owned, or exclusively in-licensed PCT patent applications and any U.S. patents issued from non-provisional applications we may file in connection with our provisional patent applications will have a statutory expiration date ranging between 2037 and 2043, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

Xilio's GPS Platform for Tumor-Activated I-O Molecules

Our proprietary engineering GPS platform enables tumor-activated I-O molecules that can effect tumor-activated immunotherapy while minimizing systemic toxicity. By masking biological agents such as cytokines, antibodies and multi-functional molecules, our GPS platform can be used to decouple therapeutic effects from toxicity for treating different cancers. As of February 15, 2023, we own one patent family covering the GPS platform in the cytokine space, including five pending U.S. patent applications and corresponding foreign applications in Europe, Japan, Australia, Brazil, Canada, China, Eurasia, Hong Kong, Indonesia, Israel, India, South Korea, Mexico, Malaysia, New Zealand, the Philippines, Saudi Arabia, Singapore and South Africa. We exclusively license two patent families relating to the GPS platform technology and our cytokine and antibody programs. One of the two patent families is exclusively in-licensed in the oncology field

from AskGene Pharma, Inc., or AskGene, and covers the GPS platform technology for cytokines. These owned and exclusively licensed patent families will have a statutory expiration date ranging between 2039 and 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

In addition, we own two patent families covering various linker designs that are used or can be used in our technology, including pending patent applications in the U.S., PCT and Taiwan.

Cytokine Programs

Our cytokine pipeline includes our clinical-stage, tumor-activated product candidates, XTX202 (IL-2) and XTX301 (IL-12).

- ***IL-2 Program.*** As of February 15, 2023, we own two patent families relating to masked IL-2 cytokines, including XTX202, with composition of matter and methods of use claims. These patent families include six pending U.S. applications, one issued U.S. patent and corresponding foreign applications in Australia, Brazil, Canada, China, Eurasian Patent Organization, European Patent Office, Hong Kong, Indonesia, Israel, India, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Saudi Arabia, Singapore, South Africa and Taiwan. The patent family exclusively in-licensed in the oncology field from AskGene also relates to the IL-2 program. These owned and exclusively in-licensed patent families will have a statutory expiration date ranging between 2039 and 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

- ***IL-12 Program.*** As of February 15, 2023, we own one patent family directed to different masked IL-12 constructs and sequences, including XTX301, with composition of matter and methods of use claims. This family includes one pending U.S. application, and corresponding foreign applications in Australia, Brazil, Canada, China, Eurasian Patent Organization, European Patent Office, Indonesia, Israel, India, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Saudi Arabia, Singapore, South Africa and Taiwan. This patent family will have a statutory expiration date in 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

Checkpoint Inhibitor Program

As of February 15, 2023, we own, co-own or exclusively in-license three patent families relating to masked anti-CTLA-4 antibody constructs and sequences, including XTX101, with composition of matter and methods of use claims. A first patent family is exclusively in-licensed from WuXi Biologics (Shanghai) Co., Ltd. and directed to anti-CTLA-4 antibodies. This family includes one allowed U.S. application and one issued U.S. patent covering certain complementarity-determining regions and variable region sequences of anti-CTLA-4 antibodies, including XTX101. Corresponding foreign applications are issued and allowed in China, Eurasia, Indonesia, Japan, South Korea, and Taiwan, and pending in Taiwan, Australia, Brazil, Canada, China, Eurasian Patent Organization, European Patent Office, Hong Kong, India, Indonesia, Israeli, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Saudi Arabia, Singapore, and South Africa. A second patent family is owned and directed to anti-CTLA-4 antibodies with modifications that improve antibody-dependent cellular cytotoxicity and includes one pending U.S. application. Corresponding foreign applications are pending in Australia, Brazil, Canada, China, Eurasian Patent Organization, European Patent Office, Hong Kong, India, Indonesia, Israeli, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Saudi Arabia, Singapore, and South Africa. A third patent family is co-owned and directed to masked anti-CTLA-4 antibodies, which includes one pending U.S. application. Corresponding foreign applications are pending in Australia, Brazil, Canada, Eurasian Patent Organization, European Patent Office, Hong Kong, India, Indonesia, Israeli, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Philippines, Saudi Arabia, Singapore, South Africa and Taiwan. In addition, we own two patent applications directed to combination therapies using masked or unmasked anti-CTLA-4 antibodies, including XTX101 and PD-1/PD-L1 antibodies. These families are presently pending as PCT and Taiwan applications. These owned, co-owned and licensed patent families will have a statutory expiration date ranging between 2037 and 2042, without taking

into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

Trademark portfolio

As of February 15, 2023, we own two federal trademark registrations for XILIO and XILIO THERAPEUTICS (Class 42) in the U.S. and a pending federal trademark application for XILIO (Class 5) in the U.S. that has been approved and published for opposition.

Patent prosecution

A PCT patent application is not eligible to become an issued patent until, among other things, we file one or more national stage patent applications within 30 months, 31 months or 32 months of the PCT application's priority date, depending on the jurisdiction, in the countries in which we seek patent protection. If we do not timely file any national stage patent applications, we may lose our priority date with respect to our PCT patent application and any potential patent protection on the inventions disclosed in such PCT patent application. Moreover, a provisional patent application is not eligible to become an issued patent. A provisional patent application may serve as a priority filing for a non-provisional patent application, we file within 12 months of such provisional patent application. If we do not timely file non-provisional patent applications, we may lose our priority date with respect to our existing provisional patent applications and any potential patent protection on the inventions disclosed in our provisional patent applications.

While we intend to timely file additional provisional patent applications and national stage and non-provisional patent applications relating to our PCT patent applications, we cannot predict whether any of our patent applications will result in the issuance of patents. If we do not successfully obtain patent protection, or if the scope of the patent protection we or our licensors obtain with respect to our product candidates, GPS platform or technology is not sufficiently broad, we will be unable to prevent others from using our technology or from developing or commercializing technology and products similar or identical to ours or other similar competing products and technologies. Our ability to stop third parties from making, using, selling, offering to sell, importing or otherwise commercializing any of our technology, inventions and improvements, either directly or indirectly, will depend in part on our success in obtaining, maintaining, defending and enforcing patent claims that cover our technology, inventions and improvements.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. The protection afforded by a patent varies on a product-by-product basis, from jurisdiction-to-jurisdiction, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of patent term adjustments and regulatory-related patent term extensions, the availability of legal remedies in a particular jurisdiction and the validity and enforceability of the patent. Moreover, patent laws and related enforcement in various jurisdictions outside of the United States are uncertain and may not protect our rights to the same extent as the laws of the United States. Changes in the patent laws and rules, whether by legislation, judicial decisions or regulatory interpretation, in the United States and other jurisdictions may diminish our ability to protect our inventions and obtain, maintain, defend and enforce our patent rights, and could therefore affect the value of our business.

The area of patent and other intellectual property rights in biotechnology is evolving and has many risks and uncertainties, and third parties may have blocking patents and other intellectual property that could be used to prevent us from commercializing our platforms and product candidates and practicing our proprietary technology. Our patent rights may be challenged, narrowed, circumvented, invalidated or ruled unenforceable, which could limit our ability to stop third parties from marketing and commercializing related platforms or product candidates or limit the term of patents that cover our platforms and product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against third parties with similar technology, and third parties may independently develop similar technologies. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any competitive advantage provided by the patent. For this and other risks related to our proprietary technology, inventions, improvements, platforms and product candidates and intellectual property rights related to the foregoing, please see the section entitled "Risk Factors—Risks Related to our Intellectual Property."

Patent term extensions

The term of individual patents depends upon the laws of the jurisdictions in which they are obtained. In most jurisdictions in which we file, the patent term is 20 years from the earliest date of filing of the first non-provisional patent application to which the patent claims priority. However, the term of U.S. patents may be extended or adjusted for delays incurred due to compliance with FDA requirements or by delays encountered during prosecution that are caused by the United States Patent and Trademark Office, or the USPTO. For example, in the United States, 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 Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, for up to five years beyond the normal expiration date of the patent. 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 in the United States. 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 for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. For more information on patent term extensions, see "Business—Government Regulation and Product Approval—Patent Term Restoration and Extension". In the future, if and when any product candidates we may develop receive FDA approval, we expect to apply for patent term extensions on issued patents covering those product candidates. Moreover, we intend to seek patent term adjustments and extensions for any of our issued patents in any jurisdiction where such adjustments and extensions are available. However, there is no guarantee that the applicable authorities, including the USPTO and FDA, will agree with our assessment of whether such adjustments and extensions should be granted, and even if granted, the length of such adjustments and extensions.

Trade secrets

In addition to patent protection, we also rely on trade secrets, know-how, unpatented technology and other proprietary information to strengthen our competitive position. We take steps to protect and preserve our trade secrets and other confidential and proprietary information and prevent the unauthorized disclosure of the foregoing, including by entering into non-disclosure and invention assignment agreements with parties who have access to our trade secrets or other confidential and proprietary information, such as employees, consultants, outside scientific collaborators, contract research and manufacturing organizations, sponsored researchers and other advisors, at the commencement of their employment, consulting or other relationships with us. In addition, we take other appropriate precautions, such as maintaining physical security of our premises and physical and electronic security of our information technology systems, to guard against any misappropriation or unauthorized disclosure of our trade secrets and other confidential and proprietary information by third parties.

Despite these efforts, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or other confidential or proprietary information. In addition, we cannot provide any assurances that all of the foregoing non-disclosure and invention assignment agreements have been duly executed, and any of the counterparties to such agreements may breach them and disclose our trade secrets and other confidential and proprietary information. Although we have confidence in the measures we take to protect and preserve our trade secrets and other confidential and proprietary information, they may be inadequate, our agreements or security measures may be breached, and we may not have adequate remedies for such breaches. Moreover, to the extent that our employees, contractors, consultants, collaborators and advisors use intellectual property owned by others in their work for us, disputes may arise as to our rights in any know-how or inventions arising out of such work. For more information, please see the section entitled "Risk Factors—Risks Related to our Intellectual Property."

License agreements

We are a party to license agreements under which we license patents, patent applications and other intellectual property from third parties. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future. We consider the following license agreements to be material to our business.

Cross-License Agreement with AskGene

In December 2020, our subsidiary, Xilio Development, entered into a cross-license agreement with AskGene Pharma, Inc., or AskGene, pursuant to which AskGene granted us certain exclusive licenses for AskGene patent rights related to non-antigen binding IL-2 products in the field of oncology and certain co-exclusive licenses for AskGene patent rights related to antigen binding IL-2 products in all fields. Under the agreement, AskGene retains rights to the AskGene patent rights in Singapore, Thailand, Malaysia, Vietnam, the People's Republic of China, Taiwan, Macau, Hong Kong, Korea and India, which we refer to as the AskGene territory, and granted licenses to us for the AskGene patent rights worldwide, excluding the AskGene territory, which we refer to as the Xilio territory.

Under the agreement, we paid AskGene an upfront payment of $6.0 million, and for any licensed IL-2 product, we are obligated to pay AskGene up to $13.0 million in the aggregate upon the achievement of specified regulatory milestones. In addition, subject to specified conditions, for any IL-2 licensed product, we are obligated to pay AskGene percentage royalties in the mid-single digits on aggregate annual net sales of IL-2 licensed products in the Xilio territory during the applicable royalty term.

In addition, we granted a non-exclusive, royalty-free, non-transferable, worldwide license to AskGene for specified Xilio patent rights related to non-antigen binding IL-2 products in the field of immunology and for specified Xilio patent rights related to antigen binding IL-2 products in all fields. Subject to the terms of the agreement and during the time period specified, we also granted AskGene an option to obtain a license in the AskGene territory to develop and commercialize our IL-2 licensed products. If AskGene exercises its option to develop and commercialize our IL-2 licensed products in the AskGene territory, then the parties will negotiate and enter into a license agreement for AskGene's exclusive development and commercialization of such products in the AskGene territory, and AskGene would be obligated to pay us percentage royalties in the mid-single digits on aggregate annual net sales of such licensed products in the AskGene territory.

During the term of the agreement, AskGene has agreed not to exploit any non-antigen binding IL-2 product comprised of specified masking technology in the field of oncology in the Xilio territory.

Subject to the terms of the agreement, each party's obligation to make royalty payments is subject to adjustment in specified circumstances and extends with respect to a licensed product in a country upon the first commercial sale of such licensed product in such country and ending upon the latest of (i) the expiration of the last valid claim of any licensed patent rights in such country that cover such licensed product, (ii) the expiration of regulatory exclusivity, if any, for such licensed product in such country, and (iii) for a specified time period following first commercial sale of such licensed product in such country.

The agreement continues on a product-by-product and country-by-country basis until the expiration of the applicable royalty term in each country, at which time the agreement expires with respect to such product in such country, and the licensed party receives a perpetual, irrevocable, fully-paid and royalty-free license to the licensed patent rights in such country. Either party has the right to terminate the agreement if the other party materially breaches the agreement and fails to cure such breach within specified cure periods or in the event the other party becomes insolvent or files for bankruptcy. Upon any termination, other than the expiration of the agreement with respect to a particular product in a particular country, the licenses granted by each party will terminate and neither party will have the right to practice the other party's patent rights.

Amended and Restated Exclusive License Agreement with City of Hope

In August 2016, our subsidiary, Xilio Development, entered into an amended and restated exclusive license agreement with City of Hope pursuant to which City of Hope granted us an exclusive worldwide license to specified patent rights related to our anti-CTLA-4 monoclonal antibody program.

For the first three licensed products or licensed services to achieve specified development and regulatory milestones, we are obligated to pay City of Hope up to $10.3 million in the aggregate per licensed product or licensed service. Subject to specified conditions, we are obligated to pay City of Hope tiered royalties in the low single digits on aggregate annual net sales of licensed products or licensed services on a country-by-country basis until the expiration of the last-to-expire patent or patent application licensed from City of Hope covering the applicable licensed product or licensed service in such country. We are also obligated to pay City of Hope a portion of any consideration we receive for the grant of sublicenses under the agreement ranging from a low to mid double-digit percentage of such consideration, subject to specified conditions under that agreement at the time that we grant any such sublicense. In addition, we paid $0.5 million to City of Hope in connection with the closing of our IPO.

The agreement continues on a country-by-country basis until the expiration of the last to expire licensed patent right in such country. We have the right to terminate the agreement for convenience at any time on 30 days' prior written notice to City of Hope. Either party has the right to terminate the agreement if the other party materially breaches the agreement and fails to cure such breach within specified cure periods. City of Hope may terminate the agreement if we or any of our affiliates or sublicensees bring specified patent challenges with respect to the licensed patents against City of Hope or if we assist others in bringing a patent challenge against City of Hope. However, instead of terminating as a result of a patent challenge, City of Hope may elect to increase our payment obligations by a specified percentage amount retroactive to the commencement of such patent challenge.

CTLA-4 Monoclonal Antibody License Agreement with WuXi Biologics

In September 2016, we entered into a license agreement with WuXi Biologics (Hong Kong) Limited, or WuXi Biologics, as amended in December 2017, pursuant to which WuXi Biologics granted us an exclusive worldwide license, including the rights to grant sublicenses through multiple tiers, to specified monoclonal antibodies and patent rights and know-how controlled by WuXi Biologics, including certain patent rights related to our anti-CTLA-4 mAb program.

For each product that incorporates a licensed antibody that has been modified using the rights licensed under the agreement, we are obligated to pay WuXi Biologics up to approximately $25.8 million in the aggregate for specified development and regulatory milestones. In addition, subject to specified conditions, we are obligated to pay WuXi Biologics tiered royalties in the low to mid-single digits on aggregate annual worldwide net sales of licensed products during the applicable royalty term and subject to early expiration or adjustment in specified circumstances. Our obligation to make royalty payments extends with respect to a licensed product in a country until the later of the expiration of the last-to-expire patent or patent application licensed from WuXi Biologics covering the applicable licensed product in such country or for a specified time period following the first commercial sale of such licensed product. Subject to specified conditions under the agreement, we also have certain obligations to contract with WuXi Biologics for specified services related to the development or manufacture of licensed products.

Unless terminated earlier in accordance with its terms, the agreement will continue until the expiration of the last to expire royalty term for a licensed product. We have the right to terminate the agreement for convenience at any time upon at least 90 days' prior written notice to WuXi Biologics. Either party may terminate the agreement for the other party's uncured material breach. Other than following our termination for convenience or termination by WuXi Biologics for our material breach, upon the expiration of the applicable royalty term for a licensed product in a country, we will receive a paid-up and royalty free license to exploit such licensed product in such country.

Manufacturing

We currently contract with a third party to manufacture our product candidates for preclinical studies and our ongoing clinical trials, and we intend to do so with one or more third parties for future preclinical studies and clinical trials. We do

not own or operate manufacturing facilities for the production of our product candidates, and we currently do not have plans to build our own clinical or commercial scale manufacturing capabilities. To date, our third-party manufacturer has met our manufacturing requirements. Our third-party manufacturer has agreed to provide clinical material meeting current good manufacturing practice, or cGMP, requirements and in sufficient quantities to meet anticipated clinical-trial demands. To meet our projected needs for commercial manufacturing, our current third-party manufacturer will need to increase its scale of production or we will need to secure one or more alternate suppliers. We believe that there are alternate manufacturers that could satisfy our anticipated clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such manufacturers, if necessary, would not result in significant delay or material additional costs.

Although we expect to rely on one or more third-party contract manufacturers for the production of our current and future product candidates, we have personnel with extensive technical, manufacturing, analytical and quality experience in biotherapeutic protein manufacturing to oversee our contract manufacturer relationships. In collaboration with our third-party manufacturer, we have manufactured cGMP clinical supply for our clinical trials for our tumor-activated, clinical-stage product candidates, XTX202 (IL-2), XTX301 (IL-12) and XTX101 (anti-CTLA-4). As we scale clinical and commercial manufacturing for each of our product candidates, we intend to continue to expand and strengthen our network of contract manufacturers to include multiple suppliers globally.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, or EU, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, sales, pricing, reimbursement, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory 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.

Review and Approval of Drugs and Biologics in the United States

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and related regulations. Biological products, or biologics, are licensed for marketing under the Public Health Service Act, or PHSA, and subject to regulation under the FDCA and related regulations. A company, institution, or organization that takes responsibility for the initiation and management of a clinical development program for such products is generally referred to as a sponsor. A sponsor seeking approval to market and distribute a new drug or biological product in the United States must typically secure the following:

- completion of preclinical laboratory tests in compliance with the FDA's good laboratory practice, or GLP, regulations and standards;

- design of a clinical protocol and submission to the FDA of an investigational new drug application, or IND, which must take effect 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 in accordance with good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug product, and with respect to biologics, the purity, potency and safety of such drug product, for each proposed indication;

- submission to the FDA of an NDA for a drug candidate product and a biologics license application, or BLA, for a biological product requesting marketing for one or more proposed indications;

- review of the request for approval by an FDA advisory committee, where appropriate or if applicable;

- completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMPs to assure the product's identity, strength, quality and purity;

- completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;

- payment of user fees and securing FDA approval of the NDA or BLA; and

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

Preclinical Studies

Before a sponsor begins testing a compound with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of the purity and stability of the manufactured substance or active pharmaceutical ingredient and the formulated product, as well as *in vitro* and animal studies to assess the safety and activity of the product candidate for initial testing in humans and to establish a rationale for therapeutic use. These studies are typically referred to as IND-enabling studies. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations and standards and the U.S. Department of Agriculture's Animal Welfare Act, if applicable. Some long-term preclinical testing, such as animal tests of reproductive AEs and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is a request for FDA authorization to administer an investigational product candidate to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biologic that is not the subject of an approved NDA or BLA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects and patients will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. The FDA's primary objectives in reviewing an IND are to assure the safety and rights of patients and to help assure that the quality of the investigation will be adequate to permit an evaluation of the drug's effectiveness and safety and of the biological product's safety, purity and potency.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. 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, or CMC. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval in the United States. Specifically, the studies must be conducted in accordance with GCP, including undergoing review and receiving approval by an independent ethics committee, or IEC, and seeking and receiving informed consent from subjects. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the trial at least annually. The IRB must review and approve, among other things, the trial protocol and informed consent information to be provided to trial subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board, or DSMB, or committee. This group provides authorization for whether a trial may move forward at designated check points based on access that only the group maintains to available data from the trial. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made based on evolving business objectives and/or competitive climate.

Human Clinical Studies in Support of an NDA or BLA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written trial protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

The clinical investigation of an investigational drug or biological product is generally divided into four phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The four phases of an investigation are as follows:

- Phase 1. Phase 1 studies include the initial introduction of an investigational new drug or biological product into humans. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational drug or biological product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.

- Phase 2. Phase 2 includes the controlled clinical trials conducted to preliminarily or further evaluate the effectiveness of the investigational drug or biological product for a particular indication(s) in patients with the disease or condition under trial, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the drug or biological product. Phase 2 trials are typically well-controlled, closely monitored, and conducted in a limited patient population.

- Phase 3. Phase 3 trials are generally controlled clinical trials conducted in an expanded patient population generally at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the drug or biological product has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug or biological product, and to provide an adequate basis for product approval.

- Phase 4. Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

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. Moreover, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate's safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are Phase 3 trials, but they may be Phase 1 or 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 December 2022, with the passage of Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious AEs occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

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

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the candidate product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health, or NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. The NIH's Final Rule on registration and reporting requirements for clinical trials became effective in 2017. Although the FDA has historically not enforced these reporting requirements due to the long delay by the Department of Health and Human Services, or HHS, in issuing final implementing regulations, the FDA has issued several Notices of Noncompliance to manufacturers since April 2021. The failure to submit required clinical trial information to clinicaltrials.gov is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues.

Expanded Access

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. FDA regulations allow access to investigational products under an IND by the sponsor 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.

There is no requirement for a sponsor to provide expanded access to an investigational product. However, if a sponsor decides to make its investigational product available for expanded access, the FDA reviews requests for expanded access and determines if treatment may proceed. Expanded access may be appropriate 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 with initiation, conduct or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

Sponsors of one or more investigational products for the treatment of a serious disease(s) or condition(s) must make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 trial; 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 an additional mechanism for patients with a life-threatening condition who have exhausted approved treatments and are unable to participate in clinical trials to access certain investigational products that have completed a Phase 1 trial, are the subject of an active IND and are undergoing investigation for FDA approval. Unlike the expanded access framework described above, the Right to Try Pathway does not require FDA to review or approve requests for use of the investigational product. There is no obligation for a manufacturer to make its investigational products available to eligible patients under the Right to Try Act.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, an application 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 investigational 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, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the 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 the 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 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 now requires the FDA to send a 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 FDA has taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population.

Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act, or FDASIA. The FDA maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population. In 2017, with the passage of the FDA Reauthorization Act of 2017, or FDARA, Congress established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an application three years after the date of enactment of that statute must submit pediatric assessments with the application if the product is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

Submission and Review of an NDA or BLA by the FDA

In order to obtain approval to market a drug or biological product in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the proposed drug product for the proposed indication, and the safety, purity and potency of the biological product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product and the safety, purity and potency of the biological product to the satisfaction of the FDA.

The application is the vehicle through which sponsors formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new product candidate must be the subject of an approved NDA or BLA before it may be commercialized in the United States. Under federal law, the submission of most applications is subject to an application user fee. The sponsor of an approved application is also subject to an annual program fee. 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. If an application is withdrawn prior to the FDA acceptance for filing, 75% of these fees may be refunded to the sponsor. If an application is withdrawn after filing, a lower portion of these fees may be refunded in certain circumstances. Currently, the fee required for the submission and review of an application for federal fiscal year 2023 is approximately $3.25 million, and the sponsor of an approved application is also subject to an annual program fee, currently more than $394,000.

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. The FDA's regulations state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the applicant. Typically, an RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety and efficacy or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. The FDA has agreed to specified performance goals in the review process of NDAs and BLAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within

ten months from the date on which FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission.

In connection with its review of an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA or BLA submission, including drug component manufacturing (e.g., active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications.

Additionally, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted to the FDA. With the passage of FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to the FDA as well as other persons holding study records or involved in the study process.

In addition, as a condition of approval, the FDA may require a sponsor to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential AEs, and whether the product is a new molecular entity. Under FDARA, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

The FDA may refer an application for a novel product to an advisory committee or explain why such referral was not made. 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.

The FDA's Decision on an NDA or BLA

The FDA reviews an application to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The term "substantial evidence" is defined under the FDCA as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product involved, on the basis of which it could fairly and responsibly be concluded by such experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical investigations to establish effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard.

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 an approval letter or a Complete Response Letter, or CRL. To issue an approval letter, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the NDA or BLA. This assessment is also informed by other factors, including: 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.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six-month extension to respond. The FDA has committed to reviewing resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. The FDA has taken the position that a CRL is not final agency action making the determination subject to judicial review.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications described in the FDA-approved labeling. Depending on the specific risk(s) to be addressed, the FDA may require that contraindications, warnings or precautions be included in the product labeling, require that post-approval trials, including Phase 4 clinical trials, be conducted to further assess a product's safety after approval, require testing and surveillance programs to monitor the product after commercialization or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing trials or surveillance programs. After approval, some 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.

Under the Ensuring Innovation Act, which was signed into law in April 2021, the FDA must publish action packages summarizing its decisions to approve new drugs and biologics within 30 days of approval of such products. To date, CRLs are not publicly available documents.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs include fast track designation, Breakthrough Therapy designation and priority review designation. None of these expedited programs changes the standards for approval but they may help expedite the development or approval process governing product candidates.

Specifically, the FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, 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.

Second, a product may be designated as a Breakthrough Therapy if it 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 product 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 help the sponsor design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of phase 4 or post-approval trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

With the passage of FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to the FDA every six months (until the study is completed), and use expedited procedures to withdraw accelerated approval of an NDA or BLA after the confirmatory trial fails to verify the product's clinical benefit. Further, FDORA requires the agency to publish on its website "the rationale for why a post-approval study is not appropriate or necessary" whenever it decides not to require such a study upon granting accelerated approval.

Post-Approval Regulation

Drugs and biologics manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with the FDA and state agencies and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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 AEs 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, suspension of the approval, or 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 NDAs or supplements to approved NDAs, 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. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. 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. 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 Department of Justice, 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. In September 2021, the FDA published final regulations that describe the types of evidence the FDA will consider in determining the intended use of a drug or biologic.

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

but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products.

Biosimilars and Regulatory Exclusivity

The 2010 Patient Protection and Affordable Care Act, or ACA, which was signed into law on March 23, 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. To date, the FDA has approved a number of biosimilars, and the first interchangeable biosimilar product was approved in July 2021, and a second product previously approved as a biosimilar was designated as interchangeable in October 2021. The FDA has also issued numerous guidance documents outlining its approach to reviewing and licensing biosimilars and interchangeable biosimilars under the PHSA.

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

Under the BPCIA, 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.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA or BLA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the Prescription Drug User Fee Act, or PDUFA, goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

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 drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different indications. If a drug or biologic 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. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a company with orphan drug exclusivity is not able to meet market demand and in cases where

a subsequent product with the same drug or biologic for the same indication 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 subsequent product to show clinical superiority in order to break the previous product's orphan drug exclusivity applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017 but have not yet been approved or licensed by FDA.

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

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of existing regulatory exclusivity. For drug products, the six-month exclusivity may be attached to the term of any existing patent or regulatory exclusivity. For biologic products, the six-month period may be attached to any existing regulatory exclusivities but not to any patent terms. This six-month exclusivity may be granted if an NDA or 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 non-patent exclusivity for drugs and biologics, or patent protection that covers a drug 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.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and the 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 approval 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 United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Pharmaceutical Coverage, Pricing and Reimbursement

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. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product 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, the product. 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.

It is time consuming and expensive to seek coverage and reimbursement from third-party payors. 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, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product candidate could reduce physician utilization once the product is approved and have a material adverse effect on 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 drug 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.

Healthcare Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug 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, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements.

Restrictions under applicable federal and state health care laws and regulations, include the 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 health care program such as Medicare and Medicaid; the federal civil and criminal false claims laws, false statements, and civil monetary penalties laws, including the civil False Claims Act, 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 Health Insurance Portability and Accountability Act, or HIPAA, which, in addition to privacy protections applicable to healthcare providers and other entities, prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs; analogous state laws and regulations, including state anti-kickback and false claims laws; and the federal transparency requirements known as the federal Physician Payments Sunshine 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 United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Effective January 1, 2022, these federal transparency reporting obligations will extend to include transfers of value made during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives. In addition, HIPAA as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, among other things, imposes limitations on certain covered healthcare providers, health plans, and healthcare clearinghouses and their respective business associates and their covered subcontractors that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information.

Further, 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 manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures or restrict financial interactions between pharmaceutical companies and healthcare providers. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction.

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. In particular, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws, govern the collection, use, disclosure, and protection of health-related and other personal information.

In addition, we may be subject to laws and regulations prohibiting bribery and corruption such as the Foreign Corrupt Practices Act, or FCPA, 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 as well as federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Violation of the laws described above or any other governmental laws and regulations may result in significant penalties, including civil, criminal, and administrative penalties, damages, fines, the curtailment or restructuring of operations, the exclusion from participation in federal and state healthcare programs, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, imprisonment, and additional reporting requirements and oversight if a manufacturer becomes subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. Furthermore, efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly.

Similar healthcare laws and regulations exist in the EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing the privacy and security of personal information

Health Care Reform in the United States and Potential Changes to Health Care Laws

Sales of any biopharmaceutical products, if and when approved by the FDA or analogous authorities outside the United States, will depend in significant part on the availability of third-party coverage and adequate reimbursement for the products.

Health care reform has been a significant trend in the U.S. health care industry and elsewhere. In particular, government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products and services. Under the former Trump administration, there were efforts to repeal or modify prior health care reform legislation and regulation and also to implement new health care reform measures, including measures related to payment for drugs under government health care programs. However, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate'' was repealed by Congress. Thus, the ACA will remain in effect in its current form. The nature and scope of health care reform in the new Biden administration remains uncertain but early actions including additional health care reform, its expressed intent to pursue certain policy initiatives to reduce drug prices, as well as challenges to actions taken under the Trump administration have been taken and are likely to continue.

There has been heightened governmental scrutiny in recent years over the manner in which manufacturers set prices for their marketed products, which has resulted in proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing and reform government program reimbursement methodologies for pharmaceutical and biologic products. For example, on August 16, 2022, the Inflation Reduction Act of 2022, or the IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B, to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

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

At the state level, legislatures are increasingly 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 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 product candidates or additional pricing pressures.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. We expect that additional federal and state health care reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for health care products and services.

Data Privacy Regulation

U.S. Privacy Law

There are multiple privacy and data security laws that may impact our business activities in the United States and in other countries where we conduct trials or where we may conduct trials or do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, for example, under HIPAA, the U.S. Department of Health and Human Services has issued regulations to protect the privacy and security of protected health information used or disclosed by specific covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. HIPAA may apply to us in certain circumstances and may also apply to our business partners in ways that may impact our relationships with them. Our clinical trials are regulated by the Federal Policy for the Protection of Human Subjects, also known as the Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. State attorneys general also have authority to enforce state privacy and security laws. Moreover, new laws and regulations governing privacy and security may be adopted in the future as well.

There have been several developments in recent years with respect to U.S. state data privacy laws. In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring

businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

General data protection regulation

Many countries outside of the United States maintain rigorous laws governing the privacy and security of personal information. The collection, use, disclosure, transfer or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or EEA, and the processing of personal data that takes place in the EEA, 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, and it imposes heightened requirements on companies that process health and other sensitive data, such as requiring in many situations that a company obtain the consent of the individuals to whom the sensitive personal data relate before processing such data. Examples of obligations imposed by the GDPR on companies processing personal data that fall within the scope of the GDPR include providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, appointing a data protection officer, 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 EEA, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States. This CJEU decision may lead to increased scrutiny on data transfers from the EU to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US Privacy Shield. The European Commission, or the EC, initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

As with other issues related to Brexit, there are open questions about how personal data will be protected in the United Kingdom and whether personal information can transfer from the EU to the United Kingdom. Following the withdrawal

of the United Kingdom from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the United Kingdom and includes parallel obligations to those set forth by GDPR. While the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the EU 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 EEA to the United Kingdom will remain lawful under GDPR. The United Kingdom government has already determined that it considers all EU 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. In addition, a recent decision from the European Commission appears to deem the United Kingdom as being "essentially adequate" for purposes of data transfer from the EU to the United Kingdom, although this decision may be re-evaluated in the future.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products.

Employees and Human Capital Resources

As of February 15, 2023, we had 89 full-time employees, including 36 employees with M.D., Pharm.D. or Ph.D. degrees. Of these full-time employees, 65 are engaged in research and development activities and 24 are engaged in general and administrative activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and developing our existing and additional employees. We are committed to diversity, equity and inclusion across all aspects of our organization, including in our recruitment, advancement and development practices. Each year, we review employee demographic information to evaluate our diversity efforts across all functions and levels of the company. We conduct annual performance and development reviews for each of our employees to discuss the individual's strengths and development opportunities, career development goals and performance goals. We also regularly survey employees to assess employee engagement and satisfaction. In addition, each regular full-time employee is provided an allowance and time to attend appropriate job-related trainings and other professional development courses, seminars, meetings, and similar sessions.

The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards. We value our employees and regularly benchmark total rewards we provide, such as short- and long-term compensation, 401(k) contributions, tuition reimbursement, health, welfare and quality of life benefits, paid time off and personal leave, against our industry peers to ensure we remain competitive and attractive to potential new hires.

Note Regarding the COVID-19 Pandemic

The impact of the COVID-19 pandemic continues to be widespread, rapidly-evolving and unpredictable on global societies, economies, financial markets, supply chains and business practices. The extent of the impact of the COVID-19 pandemic, including variants of the COVID-19 virus, on our business, operations, and clinical development timelines and plans remains uncertain. For a discussion regarding risks and uncertainties related to the impact of the COVID-19 pandemic and its potential impact on our business and financial results, please refer to our "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K.

Corporate Information

We are a Delaware corporation that was incorporated on June 18, 2020 under the name Xilio Therapeutics, Inc. We maintain a website at the following address: www.xiliotx.com. The information contained on, or that can be accessed through, our website is not incorporated by reference into this Annual Report on Form 10-K or in any other report or document we have filed or may file with the Securities and Exchange Commission, or SEC, and any reference to our website address is intended to be an inactive textual reference only.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended, or the Exchange Act. These include our Annual Reports on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. We make this information available on our website (free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC. In addition, we routinely post on the "Investors & Media" page of our website investor and scientific presentations, SEC filings, press releases, public conference calls and webcasts and other statements about our business and results of operations, some of which may contain information that may be deemed material to investors. Accordingly, investors should monitor these portions of our website, in addition to following our press releases, SEC filings, public conference calls and webcasts, as well as our social media channels (our Twitter (@xiliotx) and LinkedIn). This list of channels may be updated from time to time on our investor relations website and may include other social media channels than the ones described above. The contents of our website or these channels, or any other website that may be accessed from our website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended.

The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC at the following address: http://www.sec.gov.

Item 1A. Risk Factors

The following information sets forth risk factors that could cause our actual results to differ materially from those contained in forward-looking statements we have made in this Annual Report on Form 10-K and those we may make from time to time. You should carefully consider the risks described below, in addition to the other information contained in this Annual Report on Form 10-K and our other public filings. Our business, financial condition or results of operations could be harmed by any of these risks. The risks and uncertainties described below are not the only ones we face. Additional risks not presently known to us or other factors not perceived by us to present significant risks to our business at this time also may impair our business operations.

Risks Related to Our Limited Operating History, Financial Position and Capital Requirements

We have incurred significant operating losses since our inception and expect to incur significant losses for the foreseeable future.

We have incurred significant operating losses since our inception and have not yet generated any revenue. If our product candidates are not successfully developed and approved, we may never generate any revenue. Our net losses were $88.2 million and $75.8 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $249.1 million. To date, we have funded our operations primarily through proceeds from the sale of preferred units and convertible preferred stock, a debt financing and our initial public offering, or IPO. We have devoted substantially all of our financial resources and efforts to research and development. We are still in the early stages of development of our product candidates, and we have not completed clinical development for our clinical-stage, tumor-activated product candidates, XTX202 (IL-2), XTX301 (IL-12) or XTX101 (anti-CTLA-4), and we have not commenced clinical development for any of our other product candidates. We have not generated any revenue from product sales to date. We expect to continue to incur significant expenses and operating losses over the next several years. Our operating expenses and net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase significantly in connection with our ongoing activities, particularly as we:

- continue to advance our current research programs and conduct additional research programs;
- advance our current product candidates and any future product candidates we may develop into preclinical and clinical development;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- obtain, expand, maintain, defend and enforce our intellectual property;

- hire additional research, clinical, regulatory, quality, manufacturing and general and administrative personnel;
- establish a commercial and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- continue to discover, validate and develop additional product candidates;
- continue to expand manufacturing capacity through third-party manufacturers and manufacture increasing quantities of our current or future product candidates for use in preclinical studies, clinical trials and for any potential commercialization;
- acquire or in-license other product candidates, technologies or intellectual property; and
- incur additional costs associated with current and future research, development and commercialization efforts and operations as a public company.

Even if we successfully complete clinical trials and obtain regulatory approval for one or more of our product candidates, our product candidates may not be commercially successful. In addition, we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate revenue, we will not become profitable and may be unable to continue operations without continued funding.

We have no products approved for commercial sale and have not generated any revenue from product sales. We may never generate any revenue or become profitable and, if we achieve profitability, we may not be able to sustain it.

To date, we have not generated any revenue from our product candidates or product sales, we do not expect to generate any revenue from the sale of products for a number of years, and we may never generate revenue from the sale of products. Our ability to generate product revenue depends on a number of factors, including our ability to:

- successfully complete our ongoing and planned preclinical studies for any current or future product candidates;
- successfully receive U.S. Food and Drug Administration, or FDA, clearance for any investigational new drug application, or IND, for any current or future product candidates;
- successfully initiate and complete clinical trials for our clinical-stage product candidates and any other current or future product candidates, including all safety and efficacy studies necessary to obtain U.S. and foreign regulatory approval for our product candidates;
- establish and maintain clinical and commercial manufacturing capabilities or make arrangements with third-party manufacturers for clinical supply and commercial manufacturing;
- launch commercial sales of our products, if and when approved, whether alone or in collaboration with others;
- obtain and maintain acceptance of the products, if and when approved, by patients, the medical community and third-party payors;
- effectively compete with other therapies;
- obtain and maintain healthcare coverage and adequate reimbursement for our products, if and when approved;
- maintain a continued acceptable safety profile of our products following approval; and

- enforce and defend intellectual property rights and claims.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of expenses we may incur in connection with these activities prior to generating product revenue. In addition, we may never succeed in these activities, and, even if we do, may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product candidates or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need to obtain substantial additional capital to finance our operations and complete the development and any commercialization of any current or future product candidates. If we are unable to raise this capital when needed, we may be forced to delay, reduce or eliminate one or more of our research and development programs or other operations.

We expect to incur increasing expenses and operating losses over the next several years in connection with our ongoing research and development activities, particularly as we pursue clinical development of our product candidates, expand research efforts and preclinical activities associated with our other existing programs and discovery platform and continue to implement the additional infrastructure necessary to support our operations as a public reporting company. Our revenue, if any, will be derived from sales of products that we do not expect to be commercially available for a number of years, if at all. If we obtain marketing approval for any current or future product candidates that we develop, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. Some of these expenses may be incurred in advance of marketing approval and could be substantial.

As of December 31, 2022, we had cash and cash equivalents of $120.4 million. We believe that our existing cash and cash equivalents will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2024.

Our existing cash and cash equivalents will not be sufficient to complete development of any current or future product candidate. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt, collaborations, licensing arrangements or other sources. Adequate additional capital may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed, on attractive terms or at all, would have a negative effect on our financial condition and our ability to develop and commercialize our current and any future product candidates, and otherwise pursue our business strategy and we may be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

In addition, our cash forecasts are based on assumptions that may prove to be wrong, and we could use our available capital resources earlier than we currently expect. Changing circumstances could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional capital sooner than planned. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

Our future capital requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, results and costs of research and development for our current and future product candidates, including our ongoing and planned clinical trials for our clinical-stage product candidates;

- the scope, prioritization and number of our research and development programs;

- the scope, costs, timing and outcome of regulatory review of our product candidates;

- the costs of expanding manufacturing capacity through third-party manufacturers and securing manufacturing materials for use in preclinical studies, clinical trials and, for any product candidates for which we receive regulatory approval, use as commercial supply;

- the costs and timing of future commercialization activities for any of our product candidates for which we receive regulatory approval;

- the amount and timing of revenue, if any, received from commercial sales of any product candidates for which we receive regulatory approval;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims;

- the extent to which we may acquire or in-license other products, product candidates, technologies or intellectual property, as well as the terms of any such arrangements;

- our ability to seek, establish and maintain a collaboration to further develop XTX101, our Fc-enhanced, tumor-activated anti-CTLA-4 mAb, with a collaborator, including the financial terms and any cost-sharing arrangements of any such collaboration;

- the impacts of the COVID-19 pandemic; and

- the costs of continuing to expand our operations and operating as a public company.

We currently do not have any committed external sources of funds and adequate additional capital may not be available to us on acceptable terms, or at all. In addition, our ability to raise additional capital may be adversely impacted by potential worsening economic conditions, both inside and outside the U.S., including without limitation heightened inflation, capital market volatility, interest rate and currency rate fluctuations, any potential economic slowdown or recession, the COVID-19 pandemic (including variants of COVID-19) and geopolitical events, including trade wars or civil or political unrest. We can give no assurance that we will be able to secure additional capital to support our operations, or if such funds are available to us, that such additional funding will be sufficient to meet our needs.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to product candidates or our technology.

Unless and until we can generate a substantial amount of product revenue, we expect to seek additional capital through a combination of public or private equity offerings, debt, collaborations, licensing arrangements or other sources. Our issuance of additional securities, whether equity or debt, or the possibility of such issuance, may cause the market price of our common stock to decline, and our stockholders may not agree with our plans for additional capital or the terms of such capital. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. To the extent that we incur additional indebtedness, we would become obligated to make payments to repay the loan balance with interest. The incurrence of any additional indebtedness would result in additional payment obligations. Under our loan and security agreement with Pacific Western Bank, or PacWest, we are required to comply with certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to declare dividends, limitations on our ability to sell or dispose any part of our business or property and other operating restrictions that could adversely impact our ability to conduct our business, and any agreements governing any other indebtedness that we may incur could require us to comply with additional covenants. If we raise funds through collaborations and licensing arrangements with third parties, we may have to relinquish valuable rights, partially or fully, to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms unfavorable to us. In addition, securing additional capital would require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

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

We are a clinical-stage biotechnology company with a limited operating history upon which investors can evaluate our business and prospects. Since inception, we have devoted substantially all of our financial resources and efforts to performing research and development activities. Our approach to the discovery and development of tumor-activated product candidates using our GPS platform is unproven, and we do not know whether we will be able to develop any approved products of commercial value. In addition, each of our product candidates is either in early clinical or preclinical development, and all of our other development programs are still in discovery stages. We have not yet demonstrated an ability to successfully complete any clinical trials, obtain regulatory approvals, manufacture a commercial-scale product, or arrange for a third party to do so on our behalf, or conduct the sales and marketing activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing biopharmaceutical products.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history. As of December 31, 2022, we had federal and state net operating loss, or NOL, carryforwards of $177.5 million and $146.6 million, respectively. We do not anticipate generating revenue from sales of products for the foreseeable future, if ever, and we do not know whether or when we will generate taxable income necessary to utilize our NOLs.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change" (generally defined as a greater than 50 percentage point change (by value) in the ownership of its equity by certain stockholders over a three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income is subject to limitations. We have not yet completed a detailed study of our inception to date ownership change activity under Section 382 of the Code. As a result of our prior private placements for preferred units and convertible preferred stock, our IPO or other transactions, we may have experienced such ownership changes in the past, and we may experience such ownership changes in the future as a result of changes in our stock ownership, some of which are outside our control. As a result, if we earn net taxable income, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset such taxable income may be subject to limitations, which could result in increased future tax liability to us and could have an adverse effect on our future results of operations.

There is also a risk that due to regulatory changes, such as suspensions on the use of NOLs, or other unforeseen reasons, our existing NOLs could expire or otherwise become unavailable to offset future income tax liabilities. As described below in "Risks Related to Ownership of Our Common Stock —Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the Tax Cuts and Jobs Act of 2017, or Tax Act, as amended by the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, includes changes to U.S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future. In addition, state NOLs generated in one state cannot be used to offset income generated in another state. For these reasons, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes.

Risks Related to the Discovery and Development of Our Product Candidates

Our business is highly dependent on the success of our current product candidates, which are in the early stages of development and will require significant additional preclinical and clinical development before we can seek regulatory approval for and commercially launch a product.

Our business and future success is highly dependent on our ability to obtain regulatory approval for, and if approved, successfully launch and commercialize, our current product candidates, including our clinical-stage, tumor-activated product candidates: XTX202 (IL-2), XTX301 (IL-12) and XTX101 (anti-CTLA-4). We are currently evaluating XTX101 and XTX202 in ongoing Phase 1 clinical trials. We recently opened clinical trial sites and are actively screening patients for enrollment at a starting dose of 5.0 μg/kg (0.005 mg/kg) in monotherapy dose-escalation for our Phase 1 clinical trial

evaluating the safety and tolerability of XTX301 in patients with advanced solid tumors. Additionally, we have a portfolio of programs that are in even earlier stages of preclinical development and may never advance to clinical-stage development

Commencing clinical trials in the United States is subject to acceptance by the FDA of an IND and finalizing the trial design based on discussions with the FDA and other regulatory authorities. In the event that the FDA requires us to complete additional preclinical studies or we are required to satisfy other FDA requests prior to commencing clinical trials, the start of our clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter approval conditions than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the EU.

To date, we have only had limited interactions with the FDA regarding our clinical development plans. We may experience issues surrounding preliminary trial execution, such as delays in FDA acceptance of any future INDs, revisions in trial design and finalization of trial protocols, difficulties with patient recruitment and enrollment, quality and provision of clinical supplies, or early safety signals.

We are not permitted to market any biological product in the United States until we receive approval of a Biologics License Application, or BLA, from the FDA. We have not previously submitted a BLA to the FDA, or similar marketing application to comparable foreign regulatory authorities. A BLA must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe, pure and potent for each desired indication. A BLA must also include significant information regarding the chemistry, manufacturing and controls for the product, and the manufacturing facilities must complete a successful pre-license inspection.

FDA approval of a BLA is not guaranteed, and the review and approval process is expensive, uncertain and may take several years. The FDA also has substantial discretion in the approval process. The number and types of preclinical studies and clinical trials that will be required for BLA approval varies depending on the product candidate, the disease or the condition that the product candidate is designed to treat and the regulations applicable to any particular product candidate. Despite the time and expense associated with preclinical studies and clinical trials, failure can occur at any stage.

The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support approval. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain approval of any product candidate that we develop based on the completed clinical trials.

Generally, public concern regarding the safety of biopharmaceutical products could delay or limit our ability to obtain regulatory approval, result in the inclusion of unfavorable information in our labeling or require us to undertake other activities that may entail additional costs. We have not obtained FDA approval for any product. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for any current or future product candidates.

The success of our business, including our ability to finance our company and generate any revenue in the future, will primarily depend on the successful development, regulatory approval and commercialization of our current and any future product candidates, which may never occur. However, given our early stage of development, it will be years before we are able to demonstrate the safety and efficacy of a treatment sufficient to warrant approval for commercialization, and we may never be able to do so. If we are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize our current or any future product candidates, we may not be able to generate sufficient revenue to continue our business.

Preclinical development is uncertain. Our preclinical programs may experience delays or may never advance to clinical trials, which would adversely affect our ability to obtain regulatory approvals or commercialize these programs on a timely basis or at all, which would have an adverse effect on our business.

All our product candidates are still in the early clinical stage or preclinical stage of development, and their risk of failure is high. Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our planned INDs in the United States, or similar applications in other jurisdictions. We cannot be certain of the timely completion or outcome of our preclinical testing and studies, and we cannot predict if the FDA or other regulatory authorities will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of our programs. As a result, we cannot be sure that we will be able to submit INDs or similar applications for our current or future preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs or similar applications will result in the FDA or other regulatory authorities allowing clinical trials to begin.

Preclinical studies and clinical trials are expensive, time-consuming and difficult to design and implement, and involve uncertain outcomes. Furthermore, results of earlier preclinical studies and clinical trials may not be predictive of results of future preclinical studies or clinical trials.

The risk of failure for our current and any future product candidates is high. It is impossible to predict when or if any of our product candidates will successfully complete preclinical studies or clinical trials evaluating their safety and effectiveness in humans or will ultimately receive regulatory approval. To obtain the requisite regulatory approvals to market and sell any of our product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our product candidates are safe and effective in humans for use in each target indication. Preclinical and clinical testing is expensive and can take many years to complete, and the outcome is inherently uncertain. Failure can occur at any time during the preclinical or clinical trial process. The outcome of preclinical testing and early clinical trials may not be predictive of the results of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. In particular, while we have conducted certain preclinical studies for each of our clinical stage product candidates, we do not know whether these product candidates will perform in our clinical trials as they have performed in these prior preclinical studies. For example, in preclinical mouse models, we observed XTX101 had tumor-selective activity and tumor growth inhibition superior to that of an ipilimumab analog, and that XTX202 had comparable tumor growth inhibition to aldesleukin and non-masked IL-2, with both XTX101 and XTX202 avoiding mortality and body weight loss. However, there is no guarantee these preclinical results will be replicated in clinical trials. Similarly, there can be no assurance that interim or preliminary clinical data or results, including without limitation the preliminary intra-tumoral pharmacodynamic data reported for two patients treated with XTX202, will be predictive of future clinical data or results. Many companies in the biopharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings made while clinical trials were underway, or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events, or AEs. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in clinical trial procedures set forth in protocols, differences in the size and type of the patient populations, adherence to the dosing regimen and other clinical trial protocols, and the rate of dropout among clinical trial participants. If we fail to produce positive results in our planned and ongoing preclinical studies or clinical trials, or if we experience material changes in clinical data or results, the development timeline and regulatory approval and commercialization prospects for our product candidates, and, correspondingly, our business, financial condition and results of operations would be materially and adversely affected.

We may encounter substantial delays in the commencement or completion, or termination or suspension, of our clinical trials, which could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidate for its intended indications. We cannot guarantee that any clinical trials, including our Phase 1 clinical trial and planned Phase 2 clinical trial for XTX202, our Phase 1 clinical trial for XTX101 or our Phase 1 clinical trial for XTX301, will be conducted as planned or completed

on schedule, if at all. We may experience numerous unforeseen events during or as a result of clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- we may be unable to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to obtain regulatory authorizations to commence a clinical trial;
- we may experience issues in reaching a consensus with regulatory authorities on trial design;
- regulators or institutional review boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trial sites may deviate from a trial protocol or drop out of a trial or fail to conduct the trial in accordance with regulatory requirements;
- the number of subjects required for clinical trials of our product candidates may be larger than we anticipate or subjects may fail to enroll or remain in clinical trials at the rate we expect;
- subjects that enroll in our studies may misrepresent their eligibility or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the subject from the trial, increase the needed enrollment size for the clinical trial or extend its duration;
- subjects may choose an alternative treatment for the indication for which we are developing our product candidates, or participate in competing clinical trials;
- subjects may experience severe or unexpected drug-related adverse effects;
- clinical trials of our product candidates may produce unfavorable, inconclusive, or clinically insignificant results;
- we may decide to, or regulators or IRBs or ethics committees may require us to, make changes to a clinical trial protocol or conduct additional preclinical studies or clinical trials, or we may decide to abandon product development programs;
- we may need to add new or additional clinical trial sites;
- our third-party contractors, including those manufacturing our product candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may experience manufacturing delays, and any changes to manufacturing processes or third-party contractors that may be necessary or desired could result in other delays;
- we or our third-party contractors may experience delays due to complications resulting from the impact of public health crises, including epidemics and pandemics such as the COVID-19 pandemic;
- the cost of preclinical testing and studies and clinical trials of any product candidates may be greater than we anticipate or greater than our available financial resources;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate or we may not be able to obtain sufficient quantities of combination therapies for use in current or future clinical trials;

- reports may arise from preclinical or clinical testing of other cancer therapies that raise safety or efficacy concerns about our product candidates; and

- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond the clinical trials and testing that we contemplate, if we are unable to successfully complete clinical trials or other testing of our product candidates, if the results of these clinical trials or tests are unfavorable or are only modestly favorable or if there are safety concerns associated with any of product candidates, we may:

- incur additional unplanned costs;

- be required to suspend or terminate ongoing clinical trials;

- be delayed in obtaining marketing approval, if at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired;

- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;

- be subject to additional post-marketing testing or other requirements;

- be required to perform additional clinical trials to support approval;

- have regulatory authorities withdraw, or suspend, their approval of the drug or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;

- be subject to the addition of labeling statements, such as warnings or contraindications;

- have the product removed from the market after obtaining marketing approval;

- be subject to lawsuits; or

- experience damage to our reputation.

Conducting clinical trials in foreign countries, as we may do for our product candidates, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocols as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

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

FDA or comparable foreign regulatory authorities, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

In addition to the factors above, we may make formulation or manufacturing changes to our product candidates, in which case we may need to conduct additional preclinical studies or clinical trials to bridge our modified product candidates to earlier versions, which may be costly, time consuming and may not be successful at all.

Our failure to successfully initiate and complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates would significantly harm our business. We cannot guarantee that our clinical trials, will begin as planned or be completed on schedule, if at all, or that we will not need to restructure our clinical trials. Significant preclinical study or clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates, which may harm our business and results of operations. In addition, many of the factors that cause, or lead to, delays of clinical trials may ultimately lead to the denial of regulatory approval of our product candidates.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons. The enrollment of patients depends on many factors, including:

- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating;
- the severity of the disease under investigation;
- the patient eligibility and the inclusion and exclusion criteria defined in the protocol;
- AEs in our clinical trials and in third-party clinical trials of agents similar to our product candidates;
- the size and health of the patient population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- our ability to obtain and maintain patient consents;
- our ability to monitor patients adequately during and after treatment;
- the risk that patients enrolled in clinical trials will drop out of the trials before completion; and
- factors we may not be able to control, including the impacts of the COVID-19 pandemic, that may limit the availability of patients, principal investigators or staff or clinical sites.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because

some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial site.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, slow down or halt our product candidate development and approval process and jeopardize our ability to seek and obtain the marketing approval required to commence product sales and generate revenue, which would cause the value of our company to decline and limit our ability to obtain additional capital, if needed.

Our product candidates may cause undesirable or unexpectedly severe side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable or unexpectedly severe side effects caused by our product candidates could cause us to interrupt, delay or halt preclinical studies or could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. Traditional cytokine therapies and checkpoint inhibitors have long been associated with severe toxicities, which can be life-threatening or fatal, that have resulted in the need to dose-reduce, dose-interrupt and discontinue many patients from treatment. As has been the case with traditional I-O treatments for cancer, it is possible that there may be side effects associated with the use of our current or future product candidates. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our clinical trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

In addition, clinical trials rely on a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered when a significantly larger number of patients is exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- regulatory authorities may require a REMS plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;
- we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;
- we may be subject to regulatory investigations and government enforcement actions;
- regulatory authorities may withdraw or limit their approval of such product candidates;
- we may decide to remove such product candidates from the marketplace;

- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and

- we may suffer reputational harm.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Interim top-line and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publish interim top-line or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or "top-line" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects.

We expect to develop certain of our product candidates in combination with third-party drugs and we will have limited or no control over the safety, supply, regulatory status or regulatory approval of such drugs.

We intend to develop our clinical-stage product candidates, and likely other future product candidates, in combination with third-party cancer drugs, which may be either approved or unapproved. For example, as part of our ongoing Phase 1/2 clinical trial for XTX202, we plan to evaluate XTX202 for the treatment of solid tumors both as monotherapy and in combination with other agents potentially including, but not limited to, anti-PD-1/PD-L1 agents or tyrosine kinase inhibitors. Our ability to develop and ultimately commercialize our current product candidates, and any future product candidates, used in combination with third-party drugs will depend on our ability to access such drugs on commercially reasonable terms for clinical trials and their availability for use with our commercialized product, if approved. We cannot be certain that current or potential future commercial relationships will provide us with a steady supply of such drugs on commercially reasonable terms or at all. Any failure to maintain or enter into new successful commercial relationships, or the expense of purchasing such third-party drugs in the market, may delay our development timelines, increase our costs and jeopardize our ability to develop our current product candidates and any future product candidates as commercially viable therapies. If any of these occur, our business, financial condition, operating results, or prospects may be materially harmed.

Moreover, the development of product candidates for use in combination with another product or product candidate may present challenges that are not faced for single agent product candidates. For example, our plans to evaluate current or future product candidates in combination with other agents may result in AEs based on the combination therapy that may negatively impact the reported safety profile of the monotherapy in clinical trials. In addition, the FDA or comparable foreign regulatory authorities may require us to use more complex clinical trial designs in order to evaluate the contribution of each product and product candidate to any observed effects. It is possible that the results of such trials could show that any positive previous trial results are attributable to the third-party drug and not our product candidate. Developments related to the third-party drug may also impact our clinical trials for the combination therapy as well as our commercial prospects should we receive regulatory approval. Such developments may include changes to the third-party drug's safety or efficacy profile, changes to the availability of the third-party drug, quality, and manufacturing and supply issues with respect to the third-party drug.

If we are able to obtain marketing approval, the FDA or comparable foreign regulatory authorities may require that products used in conjunction with each other be cross labeled for combined use. To the extent that we do not have rights to the third-party drug, this may require us to work with such third party to satisfy such a requirement. We would also continue to be subject to the risks that the FDA or comparable foreign regulatory authorities could revoke approval of the third-party drug used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues

could arise with such drug. Similarly, if the third-party drugs we use in combination with our product candidates are replaced as the standard of care for the indications we choose for any of our product candidates, the FDA or comparable foreign regulatory authorities may require us to conduct additional clinical trials. The occurrence of any of these risks could result in our own products, if approved, being removed from the market or being less successful commercially.

We may not be successful in our efforts to use our GPS platform to enable the development of a pipeline of tumor-activated product candidates.

A key element of our strategy is to use our novel GPS platform to engineer and develop tumor-activated molecules with the potential to trigger anti-tumor immunity with minimal systemic toxicity in order to build a pipeline of product candidates. We may not be able to continue to identify and develop novel immuno-oncology therapies. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development. For example, potential product candidates may be shown to have harmful side effects or other characteristics that indicate that they are unlikely to or will not be drugs that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our GPS platform approach or take longer to do so than anticipated, we will not or may not be able to obtain drug revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

We may not be successful in our efforts to identify or discover additional product candidates.

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

Research programs to pursue the development of our existing and planned product candidates for additional indications and to identify new product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. We may in the future rely on third parties for certain research, and we will not have complete control over their performance and ability to successfully develop product candidates. Our research programs may initially show promise in identifying potential indications and/or 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 product candidates;

- potential 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; and

- it may take greater human and financial resources than we will possess to identify and advance additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our product portfolio.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our current product candidates or to develop suitable additional product candidates through internal research programs, which could materially adversely affect our future growth and prospects.

Our approach to the discovery and development of product candidates based on our technological approaches is unproven, and we do not know whether we will be able to develop any products of commercial value.

The success of our business depends primarily upon our ability to discover, develop and commercialize products based on our technological approaches. While we have had favorable preclinical study results related to our clinical stage product candidates, we have not yet succeeded and may not succeed in demonstrating efficacy and safety for any product candidates in current or future clinical trials or in obtaining marketing approval thereafter. We rely on matrix metalloproteases, or MMPs, to activate our molecules within the tumor microenvironment. If MMP activity in human tumors is not sufficient to cleave the masking protein domain, the potential efficacy of our product candidates would be

limited. We have no assurance that our product candidates will successfully progress from preclinical studies into clinical development and ultimately marketing approval. We have invested substantially all of our efforts and financial resources in developing our initial product candidates and our future success is highly dependent on the continued successful development of our technology and product candidates.

In addition, the clinical trial requirements of the FDA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate may vary according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates can be more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates. As a result, we may face a greater regulatory burden to initiate clinical trials or to obtain regulatory approval of our product candidates as compared to product candidates based on more established technology. In addition, any product candidates for which we may be able to obtain marketing approval may be subject to extensive post-approval regulatory requirements, including requirements pertaining to manufacturing, distribution and promotion. We may need to devote significant time and resources to compliance with these requirements.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

We have chosen to initially develop each of our clinical-stage product candidates for the treatment of various solid tumor types. Nevertheless, our development efforts will be limited to a small number of cancer types, and we may forego or delay pursuit of opportunities in other cancer types that may prove to have greater potential. Likewise, we may forego or delay the pursuit of opportunities with other potential product candidates that may prove to have greater commercial potential.

In addition, our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any viable product candidates. Similarly, if we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

We may become exposed to costly and damaging liability claims, either when testing our product candidates in the clinic or following commercial sale, and any product liability insurance we may obtain may not cover all damages from such claims.

We are exposed to potential product liability risks that are inherent in the research, development, manufacturing, marketing and use of biopharmaceutical products. The use of product candidates by us in clinical trials, and any sale of approved products in the future, may expose us to liability claims. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical trials, 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 product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts.

Although the clinical trial process is designed to identify and assess potential side effects, it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If any of our product candidates were to cause adverse side effects during clinical trials or after approval thereof, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or cease the development or commercialization of our product candidates or any products for which we may have received marketing approval. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- delay or termination of clinical trials;

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media and social media attention;
- withdrawal of clinical trial participants or difficulties in recruiting new trial participants;
- initiation of investigations by regulators;
- costs to defend or settle 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;
- significant negative financial impact; and
- the inability to commercialize any of our product candidates, if approved.

Although we will seek to procure and maintain product liability insurance coverage, we may be unable to secure such insurance, and any insurance coverage we obtain may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage each time we commence a clinical trial and if we successfully commercialize any product candidate. As the expense of insurance coverage is increasing, we may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If a successful product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be materially harmed.

Risks Relating to Manufacturing and Supply

Manufacturing biologics is complex, and we may experience manufacturing problems that result in delays in our development or commercialization programs.

The manufacturing of biologics is complex and difficult and we may experience production issues or interruptions for our product candidates, including raw material or starting material variability in terms of quality, cell line viability, productivity or stability issues, shortages of any kind, shipping, distribution, storage and supply chain failures, growth media contamination, equipment malfunctions, operator errors, facility contamination, labor problems, natural disasters, disruption in utility services, terrorist activities, or acts of god that are beyond our control or the control of our contract manufacturers, or CMOs.

Given the nature of biologics manufacturing, there is a risk of contamination during manufacturing. Any contamination could materially harm our ability to produce product candidates on schedule and could harm our results of operations and cause reputational damage. Some of the raw materials that we anticipate will be required in our manufacturing process are derived from biologic sources. Such raw materials may be difficult to procure and may be subject to contamination or recall.

Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims, insufficient inventory or potentially delay progression of our preclinical or clinical development of any product candidates we may develop. If we successfully develop product candidates, we may encounter problems achieving adequate quantities and quality that meet FDA, European Medicines Agency, or EMA, or other comparable applicable foreign standards or specifications with consistent and acceptable production yields and costs. The ability to scale our manufacturing and maintain the manufacturing process at the same levels of quality and efficacy that we are currently manufacturing is yet to be tested. If

we or our third-party CMOs are unable to scale our manufacturing at the same levels of quality and efficiency, we may not be able to supply the required number of doses for clinical trials or commercial supply. A material shortage, contamination or manufacturing failure in the manufacture of any product candidates we may develop or other adverse impact or disruption in the commercial manufacturing or the production of clinical material could materially harm our development timelines and our business, financial condition, results of operations and prospects.

We face risk related to our reliance on our current and any future CMOs. For example, we and our CMOs are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities of the CMOs on which we rely may not continue to meet regulatory requirements, may have limited capacity or may experience interruptions in supply, any of which could adversely affect our development and commercialization plans for our product candidates. All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including any CMOs of any product candidates we may develop, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials must be manufactured in accordance with clinical Good Manufacturing Practices, or cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our CMO must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's current Good Laboratory Practices and current Good Manufacturing Practices regulations enforced through its facilities inspection program. Our facilities and quality systems and the facilities and quality systems of our CMOs must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of any product candidates we may develop or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our CMOs. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any CMO with which we contract for manufacturing and supply fails to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

Currently, we depend on a single manufacturer for the manufacturing processes required to develop our product candidates. We cannot ensure that this manufacturer will remain in business or have sufficient capacity or supply to meet our needs. Our use of a single manufacturer exposes us to several risks, including price increases or manufacturing delays beyond our control. This CMO has significant operations in China, which subjects us to additional risks including those related to U.S. export control laws. Moreover, reliance on third-party manufacturers generally entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms or at all, particularly if they are affiliated with our competitors;

- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities, particularly if they are under contract with our competitors;

- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;

- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier;

- the inability to obtain components or materials from alternate sources at acceptable prices in a timely manner; and

- substantial delays or difficulties related to the establishment of replacement manufacturers who meet regulatory requirements.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

Additionally, if supply from one approved manufacturer is interrupted, such as could be the case with our current CMO, there could be a significant disruption in supply. While we believe there are alternate manufacturers who can provide the manufacturing processes required to develop our product candidates, if we have to switch to a replacement manufacturer, the manufacture and delivery of our product candidates could be interrupted for an extended period, which could adversely affect our business. Furthermore, an alternative manufacturer may need to modify the manufacturing process required to develop our product candidates and would need to be qualified through additional regulatory filings, which could result in further delay and significant costs. The regulatory agencies may also require additional studies or trials if a new manufacturer is relied upon for clinical or commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, 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 or we could lose potential revenue.

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

We and any CMOs and suppliers we engage are subject to numerous federal, state and local environmental, health, and safety laws, regulations and permitting requirements, including those governing laboratory procedures; the generation, handling, use, storage, treatment and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air and water; and employee health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Under certain environmental laws, we could be held responsible for costs relating to any contamination at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our research and product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or

contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws, regulations and permitting requirements. These current or future laws, regulations and permitting requirements may impair our research, development or production efforts. Failure to comply with these laws, regulations and permitting requirements also may result in substantial fines, penalties or other sanctions or business disruption, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Any third-party CMOs and suppliers we engage will also be subject to these and other environmental, health and safety laws and regulations. Liabilities they incur pursuant to these laws and regulations 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.

Risks Related to our Dependence on Third Parties

We expect to rely on third parties to conduct, supervise and monitor IND-enabling studies and clinical trials, and if these third parties perform in an unsatisfactory manner, it may harm our business, reputation and results of operations.

We expect to rely on CROs and research and clinical trial sites to ensure our IND-enabling studies and clinical trials are conducted properly and on time, and we expect to rely in the future on CROs for additional research programs. While we will have agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of these studies 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 will be required to comply with the FDA's Good Clinical Practices, or GCPs, for conducting, recording and reporting the results of IND-enabling studies and clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these GCPs through periodic inspections of study sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the preclinical and clinical data generated in our studies may be deemed unreliable and the FDA may require us to perform additional studies before approving any marketing applications. Upon inspection, the FDA may determine that our studies did not comply with GCPs.

Our CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols or regulatory requirements, or for any other reasons, our studies may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize any product candidates we may develop. As a result, our financial results and commercial prospects would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We may enter into collaborations, licenses or similar arrangements with third parties for the research, development and commercialization of certain of our current or future product candidates. If any such arrangements are not successful, we may not be able to capitalize on the market potential of those product candidates.

We may seek third-party collaborators or licensors for the research, development and commercialization of certain of our current or future product candidates. If we enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of any product candidates we may seek to develop with them. Our ability to generate revenues from

these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any collaboration that we enter into.

Collaborations, licenses or similar arrangements involving our research programs or any product candidates pose numerous risks to us, including the following:

- collaborators or licensors have significant discretion in determining the efforts and resources that they will apply to these arrangements;
- collaborators or licensors may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the such third party's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators or licensors may delay programs, preclinical studies or clinical trials, provide insufficient funding for programs, preclinical studies or clinical trials, stop a preclinical study or clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators or licensors could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators or licenses may be acquired by a third party having competitive products or different priorities;
- collaborators or licensors with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidate(s);
- collaborators or licensors may not properly obtain, maintain, enforce or defend our intellectual property or proprietary rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- disputes may arise between the collaborators or licensors and us that result in the delay or termination of the research, development, or commercialization of our product candidates or any of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources;
- we may lose certain valuable rights under certain circumstances, including if we undergo a change of control;
- collaborations or licenses may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates; and
- collaborations or license agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator or licensor of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.

If we enter into collaborations, licenses or similar transactions and such arrangements do not result in the successful development and commercialization of product candidates, or if one of our collaborators or licensors terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under such agreement. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to find a suitable replacement collaborator or licensor or

for us to attract new collaborators or licensors, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K apply to the activities of our collaborators or licensors.

These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators, and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration or license agreement will depend, among other things, upon our assessment of the resources and expertise of such third-party collaborator or licensor and the terms and conditions of the proposed collaboration or license. Further, if we license rights for use in any product candidates we or our collaborators may develop, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

If we are not able to establish collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our product development and research programs and the potential commercialization of any product candidates we may develop will require substantial additional cash to fund expenses. For some of the product candidates we may develop, we may decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates. For example, we plan to continue to explore strategic opportunities to advance XTX101 with a partner beyond the current Phase 1 clinical trial.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, the EMA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidates for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay their potential commercialization, reduce the scope of any sales or marketing activities, or increase our own expenditures on the development of the applicable product candidate.

Certain of our research and development and manufacturing activities take place in China through third-party CROs, collaborators or manufacturers. A significant disruption in the operation of those CROs, collaborators or manufacturers could materially adversely affect our business, financial condition and results of operations.

We have relied on certain third parties located in China to manufacture and supply certain raw materials used in our product candidates, and we expect to continue to use such third-party manufacturers for such purposes. A natural disaster, epidemic or pandemic, including the recent COVID-19 pandemic, trade war, political unrest, economic conditions, changes in legislation, including the passage of the People's Republic of China Biosecurity law, which became effective on April 15, 2021, and subsequent legislation that China may adopt in the future, or other events in China could disrupt the business or operations of CROs, collaborators, manufacturers or other third parties with whom we conduct business now or in the

future. Any disruption in China that significantly impacts such third parties, including services provided by CROs for our research and development programs, or our manufacturers' ability to produce raw materials in adequate quantities to meet our needs could impair our ability to operate our business on a day-to-day basis and impede, delay, limit or prevent the research, development or commercialization of our current and future products or product candidates. In addition, for any activities conducted in China, we are exposed to the possibility of product supply disruption and increased costs in the event of changes in the policies of the U.S. or Chinese governments, political unrest or unstable economic conditions including sanctions in China or changes in U.S. export laws, and we may be exposed to fluctuations in the value of the local currency in China for goods and services. Our costs for any of these services or activities could also increase as a result of future appreciation of the local currency in China or increased labor costs if the demand for skilled laborers increases and/or the availability of skilled labor declines in China.

Risks Related to Commercialization

We have never commercialized a product candidate and we may lack the necessary expertise, personnel and resources to successfully commercialize any products that receive regulatory approval, either on our own or together with collaborators.

We have never commercialized a product candidate. We currently have no sales force or marketing or distribution capabilities. To achieve commercial success of our product candidates, if any are approved, we will have to develop our own sales, marketing and supply capabilities or outsource these activities to one or more third parties. Factors that may affect our ability to commercialize our product candidates on our own include our ability to recruit and retain adequate numbers of effective sales and marketing personnel and obtain access to or persuade adequate numbers of physicians to prescribe our product candidates, as well as any unforeseen costs we may incur in connection with creating an independent sales and marketing organization. Developing a sales and marketing organization requires significant investment and substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which could delay the launch of our product candidates. We may not be able to build an effective sales and marketing organization in the United States, the EU or other key global markets. To the extent we need to rely upon one or more third parties, we may have little or no control over the marketing and sales efforts of those third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We will also face competition in any search for third parties to assist us with sales and marketing efforts for our product candidates. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of our product candidates, we may have difficulties generating revenue from them.

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new products is highly competitive. We face competition with respect to our current product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical, specialty pharmaceutical and biotechnology companies among others. We compete in the segments of the pharmaceutical, biotechnology and other related markets that develop immunotherapies for the treatment of cancer. There are other companies working to develop immunotherapies for the treatment of cancer including divisions of pharmaceutical and biotechnology companies of various sizes. Some of these competitive therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We are developing our current product candidates for the treatment of cancer and have not completed clinical development for our clinical-stage, tumor-activated product candidates, XTX202 (IL-2), XTX301 (IL-12) or XTX101 (anti-CTLA-4), and we have not commenced clinical development for any of our other product candidates or received marketing approval for any of our product candidates. There are already a variety of available therapies marketed for cancer and some of the currently approved therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved therapies are well-established and widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. We expect that if our product

candidates are approved, they will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates. Competition may further increase with advances in the commercial applicability of technologies and greater availability of capital for investment in these industries.

XTX202, if approved, may face competition from other IL-2-based cancer therapies. For example, Proleukin (aldesleukin), a synthetic protein very similar to IL-2, is approved and marketed for the treatment of metastatic renal cell carcinoma and melanoma. In addition, we are aware that a number of other companies have modified or low-dose IL-2 programs in development for the treatment of cancer, including Alkermes plc, Anaveon AG, Ascendis Pharma A/S, Asher Biotherapeutics, Inc., Aulos Bioscience, Inc., Bright Peak Therapeutics, Cue Biopharma, Inc., Cugene Inc., Cullinan Management Inc., Egle Therapeutics SAS, GI Innovation, Iovance Biotherapeutics, Inc., Kymab Ltd., Medicenna Therapeutics Corp., Medikine, Inc., Modulate Therapeutics, Inc., Neoleukin Therapeutics, Inc., Philogen S.p.A., Proviva Therapeutics, Inc., Roche AG, Sanofi, Selecxine, Synthekine, Inc., Trutino Biosciences Inc., Werewolf Therapeutics, Inc., XOMA Corporation and Zydus Cadila.

With respect to XTX301, there are no approved IL-12 therapies currently on the market for the treatment of cancer; however, we are aware of several other companies that have modified IL-12 or intra-tumoral IL-12 delivery programs for the treatment of cancer in development, including Amunix Pharmaceuticals, Inc., AstraZeneca plc / Moderna, Inc., Cullinan Management Inc., Dragonfly Therapeutics, Inc., ImmunityBio, Inc., PDS Biotechnology Corporation, Philogen S.p.A., Sonnet BioTherapeutics, Werewolf Therapeutics, Inc., Xencor Inc. and Zymeworks Inc.

XTX101, if approved, may face competition from other anti-CTLA-4 based therapies. For example, Yervoy (ipilimumab), an anti-CTLA-4, is approved to treat melanoma, renal cell carcinoma and certain cancers of the large intestine, and Imjudo (tremelimumab) is approved as a combination therapy to treat unresectable hepatocellular carcinoma. In addition, we are aware that several companies have anti-CTLA-4 programs in development, including Adagene, Inc., Agenus Inc., AstraZeneca plc, BeiGene, Ltd., Bristol-Myers Squibb Inc., CytomX Therapeutics, Inc. and MacroGenics, Inc.

Our competitors may succeed in developing, acquiring or licensing, on an exclusive basis, products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. We also compete with these organizations in establishing clinical trial sites and patient registration for clinical trials, as well as in recruiting and retaining qualified scientific and management personnel, which could negatively affect our level of expertise and our ability to execute our business plan.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. Established pharmaceutical companies may invest heavily to accelerate discovery and development of novel product candidates or to in-license novel product candidates that could make our product candidates less competitive or obsolete. Smaller or early-stage companies may also prove to be significant competitors, including through collaborative arrangements with large and established companies. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. The availability of competing products could limit the demand and the price we are able to charge for product candidates we commercialize, if any. The inability to compete with existing or subsequently introduced products would harm our business, financial condition and results of operations.

If we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, the commercialization of any of our product candidates may be delayed, and our business could be harmed.

For planning purposes, we sometimes estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies and clinical trials, the submission of regulatory filings or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the completion of an ongoing clinical trial, the initiation of other clinical trials, receipt of regulatory approval or the commercial launch of a product. The achievement of many of these milestones may be outside of our control. All of these milestones are based on

a variety of assumptions which may cause the timing of achievement of the milestones to vary considerably from our estimates, including:

- our available capital resources or capital constraints we experience;
- the rate of progress, costs and results of our clinical trials and research and development activities, including the extent of scheduling conflicts with participating clinicians and collaborators;
- our ability to identify and enroll patients who meet clinical trial eligibility criteria;
- our receipt of approvals by the FDA, EMA and comparable regulatory authorities in other jurisdictions, and the timing thereof;
- other actions, decisions or rules issued by regulators;
- our ability to access sufficient, reliable and affordable supplies of materials used in the manufacture of our product candidates;
- our ability to manufacture and supply clinical trial materials to our clinical trial sites on a timely basis;
- the efforts of our collaborators with respect to the commercialization of our product candidates; and
- the securing of, costs related to, and timing issues associated with, commercial product manufacturing as well as sales and marketing activities.

If we fail to achieve announced milestones in the timeframes we expect, the commercialization of any of our product candidates may be delayed, and our business, results of operations, financial condition and prospects may be adversely affected.

If approved, our product candidates that are licensed and regulated as biological products, or 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 ACA, to establish an abbreviated pathway for the approval of biosimilar and interchangeable with an FDA-licensed reference biologic product. 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, reference biological product is granted 12 years of non-patent 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 approval 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 their BLA does not rely on the reference product or 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 that is approved in the United States 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 candidate to be a reference product 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 is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. The approval of a biosimilar of our product candidates could have a material adverse impact on our business due to increased competition and pricing pressure.

If competitors are able to obtain regulatory approval for biosimilars referencing our product candidates, our product candidates may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

The sizes of the potential markets for our product candidates are difficult to estimate and, if any of our assumptions are inaccurate, the actual markets for our product candidates may be smaller than our estimates.

The potential market opportunities for our product candidates are difficult to estimate and, if our product candidates are approved, will ultimately depend on, among other things, the indications for which our product candidates are approved for sale, any products with which our product candidates are co-administered, the success of competing therapies and therapeutic approaches, acceptance by the medical community, patient access, product pricing, reimbursement and our ability to create meaningful value propositions for patients, prescribers and payors. Our estimates of the potential market opportunities for our product candidates are predicated on many assumptions, which may include industry knowledge and publications, third-party research reports and other surveys. Although we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain, and their reasonableness has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

The successful commercialization of our product candidates will depend in part on the extent to which we obtain and maintain favorable insurance coverage, adequate reimbursement levels and cost-effective pricing policies with third-party payors.

The availability and adequacy of coverage and reimbursement by third-party payors, including governmental healthcare programs such as Medicare and Medicaid, managed care organizations, and private health insurers, are essential for most patients to be able to afford prescription medications such as our product candidates, if approved. Our ability to achieve acceptable levels of coverage and reimbursement for products by third-party payors will have an effect on our ability to successfully commercialize our product candidates. We cannot be sure that coverage and reimbursement in the United States, the EU or elsewhere will be available for our product candidates, if approved, or any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs or biologics when an equivalent generic drug, biosimilar or a less expensive therapy is available. It is possible that a third-party payor may consider our product candidates as substitutable and only offer to reimburse patients for the less expensive product. Even if we show improved efficacy or improved convenience of administration with our product candidates, pricing of existing third-party therapeutics may limit the amount we will be able to charge for our product candidates. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in our product candidates, if approved. Even if our product candidates are approved and we obtain coverage for our product candidates by a third-party payor, such products may not be considered cost-effective and/or the resulting reimbursement payment rates may be insufficient or may require co-payments that patients find unacceptably high. Interim reimbursement levels for new medicines, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Net prices for medicines 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 medicines from countries where they may be sold at lower prices than in the United States. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved, and may not be able to obtain a satisfactory financial return on our product candidates.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. The regulations that govern marketing approvals, pricing and reimbursement for new medicines vary widely from country to

country. In the United States, third-party payors play an important role in determining the extent to which new drugs and biologics will be covered. The Medicare and Medicaid programs increasingly are used as models in the United States for how third-party payors develop their coverage and reimbursement policies for drugs and biologics. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. We cannot predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates, if approved.

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States and coverage and reimbursement for products can therefore differ significantly from payor to payor and coverage and reimbursement by one payor does not guarantee coverage and reimbursement by another payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Our ability to demonstrate to these third-party payors that any of our approved product candidates creates a meaningful value proposition for patients, prescribers and payors will be important to gaining market access and reimbursement and there is no guarantee that we will be successful in doing so. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases on short notice, and we believe that changes in these rules and regulations are likely.

Even if a product candidate we develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, hospitals, cancer treatment centers, third-party payors and others in the medical community necessary for commercial success.

If any product candidate we develop receives marketing approval, whether as a single agent or in combination with other therapies, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, hospitals, cancer treatment centers, third-party payors, and others in the medical community. For example, cancer treatments like chemotherapy, radiation therapy and certain existing immunotherapies are well established in the medical community, and doctors may continue to rely on these therapies. If the product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable.

The degree of market acceptance of any product, if approved for commercial sale, will depend on a number of factors, including:

- the product's efficacy, safety and potential advantages compared to alternative treatments;
- the prevalence and severity of any side effects;
- the product's convenience and ease of administration compared to alternative treatments;
- the clinical indications for which the product is approved;
- the willingness of the target patient population to try a novel treatment and of physicians to prescribe such treatments;
- the recommendations with respect to the product in guidelines published by scientific organizations;
- the ability to obtain sufficient third-party insurance coverage and adequate reimbursement, including, if applicable, with respect to the use of the product as a combination therapy;
- the strength of marketing, sales and distribution support;
- the effectiveness of our sales and marketing efforts;
- the approval of other new products for the same indications; and

- our ability to offer the product for sale at competitive prices.

If we obtain marketing approval for a product but such product does not achieve an adequate level of market acceptance, we may not generate or derive significant revenue from that product and our business, financial condition and results of operations may be adversely affected.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for any product candidates we develop or for other proprietary technologies we may develop, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize product candidates and technology similar or identical to our product candidates and technology, and our ability to successfully commercialize any product candidates we may develop, and our technology may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates, their respective components, formulations, combination therapies, methods used to manufacture them and methods of treatment and development that are important to our business. If we do not adequately protect our intellectual property rights, competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our product candidates that are important to our business; we also license and may in the future license or purchase additional patents and patent applications filed by others. If we are unable to secure or maintain patent protection with respect to our product candidates and any proprietary products and technology we develop, our business, financial condition, results of operations and prospects could be materially harmed.

We cannot provide any assurances that any of our patents have, or that any of our pending patent applications that mature into issued patents will include, claims with a scope sufficient to protect our current and future product candidates or otherwise provide any competitive advantage. Specifically, our patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, a third party may develop a competitive therapy that provides benefits similar to one or more of our product candidates but that uses a different masking moiety that falls outside the scope of our patent protection. If the patent protection provided by the patents and patent applications we hold or have licensed with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business.

The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. The United States Patent and Trademark Office, or the USPTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. Our or our licensor's failure to comply with all such provisions during the patent process could result in abandonment or lapse of a patent or patent application that we own or license, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market and compete with us earlier than would otherwise have been the case. Moreover, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. In addition, to the extent that we license intellectual property in the future, we cannot guarantee that those licenses will remain in force.

Patent positions of life sciences companies can be uncertain and involve complex factual and legal questions and has in recent years been the subject of much litigation. No consistent policy governing the scope of claims allowable in the field of engineered therapeutic proteins has emerged in the United States. The scope of patent protection in jurisdictions outside of the United States is also uncertain. Changes in either the patent laws or their interpretation in any jurisdiction that we seek patent protection may diminish our ability to protect our inventions, maintain and enforce our intellectual property rights; and, more generally, may affect the value of our intellectual property, including the narrowing of the scope of our patents and any that we may license. Under the America Invents Act enacted in 2011, or the AIA, the United States moved

to a first-to-file system in early 2013 (whereby, assuming the other requirements for patentability are met, the first to file a patent application is entitled to the patent), from the previous system under which the first to make a claimed invention was entitled to the patent. Publications of discoveries in the scientific and academic literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to file for patent protection on the inventions claimed in our patents or pending patent applications. Furthermore, for U.S. applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the USPTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. We cannot be certain that we are the first to invent the inventions covered by pending patent applications and, if we are not, we may be subject to priority disputes. We may be required to disclaim part or all of the term of certain patents or all of the term of certain patent applications.

The patent prosecution process is complex, expensive, time-consuming and inconsistent across jurisdictions. We may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent rights at a commercially reasonable cost or in a timely manner. In addition, we may not pursue or obtain patent protection in all relevant markets. It is possible that we will fail to identify important patentable aspects of our research and development efforts in time to obtain appropriate or any patent protection. While we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development efforts, including for example, our employees, external academic scientific collaborators, CROs, CMOs, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose our confidential or proprietary information before a patent application is filed, thereby endangering our ability to seek patent protection.

The issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. Pending patent applications cannot be enforced against third parties unless, and until, patents issue from such applications, and then only to the extent the issued claims cover the technology. There can be no assurance that our patent applications or any patent applications that we may license in the future will result in patents being issued. Further, the scope of the invention claimed in a patent application can be significantly reduced before the patent is issued, and this scope can be reinterpreted after issuance. Even if patent applications we currently own or that we may license in the future issue as patents, they may not issue in a form that will provide us with adequate protection to prevent competitors or other third parties from competing with us, or otherwise provide us with a competitive advantage. Any patents that eventually issue may be challenged, narrowed or invalidated by third parties. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by valid and enforceable patent rights. Our competitors or other third parties may be able to evade our patent rights by developing new products that are similar to our product candidates, biosimilars of our product candidates, or alternative technologies or products in a non-infringing manner.

The issuance or grant of a patent is not irrefutable as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. There may be prior art of which we are not aware that may affect the validity or enforceability of a patent claim. There also may be prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. We may in the future, become subject to a third-party pre-issuance submission of prior art, pre- or post-issuance opposition, derivation, revocation, re-examination, post-grant and inter partes review, or interference proceeding and other similar proceedings challenging our patent rights or the patent rights of others in the U.S. Patent and Trademark Office, or USPTO, or other foreign patent office. An unfavorable determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us.

Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Moreover, third parties may have certain ownership interest in some of our owned and in-licensed patents and patent applications. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our

competitors, and our competitors could market competing products and technology. In addition, we or our licensors may need the cooperation of any such co-owners of our owned and in-licensed patents in order to enforce such patents against third parties, and such cooperation may not be provided to us or our licensors. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Some of our patent applications have been granted or may be granted or allowed in the future. We cannot be certain that an allowed patent application will become an issued patent. There may be events that can cause the allowance of a patent application to be withdrawn. For example, after a patent application has been allowed, but prior to being issued, material that could be relevant to patentability may be identified. In such circumstances, the sponsor may pull the application from allowance in order for the USPTO to review the application in view of the new material. We cannot be certain that the USPTO will re-allow the application in view of the new material. Further, periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and following the issuance of a patent. We rely on our outside counsel and other professionals or our licensing partners to pay these fees due to the USPTO and non-U.S. government patent agencies and to help us comply with other procedural, documentary and other similar requirements and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

Issued patents covering our product candidates or technology could be found invalid or unenforceable if challenged in court or the USPTO.

Despite the measures we take to obtain and maintain patent and other intellectual property rights with respect to our product candidates, our intellectual property rights could be challenged or invalidated. If we or one of our licensors initiate legal proceedings against a third party to enforce a patent covering one of our product candidates or our technology, the defendant could counterclaim that the patent covering our product candidate or technology, as applicable, is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, inter partes review, post-grant review and equivalent proceedings in foreign jurisdictions (such as opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates or technology. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our patent counsel and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, or if we are otherwise unable to adequately protect our rights, we would lose at least part, and perhaps all, of the patent protection on our product candidates or technology. Such a loss of patent protection could have a material adverse impact on our business and our ability to commercialize or license our technology and product candidates.

Changes to patent law in the United States and in foreign jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and

legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States continues to adapt to wide-ranging patent reform legislation that became effective starting in 2012. Moreover, recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty regarding our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on new legislation and decisions by the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, although currently under review by the U.S. Supreme Court, in the case *Amgen v. Sanofi*, the Federal Circuit held that broad functional antibody claims are invalid for lack of enablement. In addition, in the *Juno v. Kite*, the Federal Circuit held broad antibody and chimeric antigen receptor claims supported by few examples invalid for lack of written description. While we do not believe that any of the patents owned or licensed by us will be found invalid based on these decisions, we cannot predict how future decisions by the courts, Congress or the USPTO may impact the value of our patents. Similarly, changes in the patent laws of other jurisdictions could adversely affect our ability to obtain and effectively enforce our patent rights, which would have a material adverse effect on our business and financial condition.

We have limited foreign intellectual property rights and may not be able to protect our intellectual property rights throughout the world.

We have obtained allowed patents in the United States that we consider to be important for certain of our product candidates, however, we may have less robust intellectual property rights outside the United States, and, in particular, we may not be able to pursue generic coverage of our product candidates outside of the United States. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Most of our patent portfolio is at the very early stage. We will need to decide whether and in which jurisdictions to pursue protection for the various inventions in our portfolio prior to applicable deadlines.

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

In addition, many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. Many countries also limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business and financial condition may be adversely affected.

We rely on in-license agreements for patent rights with respect to our product candidates and may in the future acquire or in-license additional third-party intellectual property rights on which we may similarly rely. We face risks with respect to such reliance, including the risk that we could lose these rights that are important to our business if we fail to comply with our obligations under these licenses or that we may be unable to acquire or in-license third-party intellectual property that may be necessary or important to our business operations.

We rely on third-party license agreements pursuant to which we have non-exclusive and exclusive rights to technology that is incorporated into our development programs and product candidates. For example, under our cross-license agreement with AskGene, we have exclusively in-licensed patent rights relating to our IL-2 program. In addition, under our license agreement with City of Hope, we have exclusively in-licensed certain patent rights that cover our anti-CTLA-4 antibody. We also have a license agreement with WuXi Biologics (Hong Kong) Limited, or WuXi Biologics, pursuant to which we received an exclusive worldwide license to specified monoclonal antibodies, or mAbs, and patent rights and know-how controlled by WuXi Biologics, including certain patent rights related to our anti-CTLA-4 mAb program. These license agreements impose diligence, milestone payment, royalty payment and other obligations on us.

Moreover, the growth of our business may depend in part on our ability to acquire, in-license or use additional third-party intellectual property rights. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. Licenses to additional third-party intellectual property, technology, processes, and materials that may be required for the development and commercialization of our product candidates or technology may not be available at all or on commercially reasonable terms. In that event, we may be required to expend significant time and resources to redesign our product candidates or manufacturing processes, or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize our future product candidates or technologies, which could materially harm our business, financial condition, results of operations and growth prospects.

In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, in the event we do in-license third-party intellectual property rights, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

Under our agreement with City of Hope, we are responsible for the achievement of certain diligence milestones, and our failure to timely achieve such milestones could result in City of Hope's termination of the agreement or conversion of our exclusive licenses under the licensed patents to non-exclusive licenses. If City of Hope terminates the agreement or converts our licenses to non-exclusive licenses as a result of our failure to meet these diligence milestones, then our ability to commercialize products comprising our anti-CTLA-4 antibody may be impaired or we may face increased competition in the commercialization of anti-CTLA-4 antibody products. Furthermore, our agreement with City of Hope is subject to, and we expect our future license agreements may also be subject to, a reservation of rights by one or more third parties, including the licensor.

Under our agreement with AskGene, AskGene retained co-exclusive rights to exploit antigen-binding IL-2 and IL-15 products. Therefore, AskGene could develop and commercialize one or more antigen-binding IL-2 or IL-15 products on a more timely basis than us, if we ever develop such a product, or that are more effective or have more commercial success than products that we may develop. Additionally, AskGene is responsible for prosecution and maintenance of the licensed patents under the agreement and any future third party from whom we may license patent rights may similarly be responsible for prosecution and maintenance of such patents. We have limited control over the activities that are the responsibility of AskGene and would have limited control over the activities that are the responsibility of any future licensor, and it is possible that prosecution and maintenance of licensed patents by AskGene or any future licensor may be less vigorous than had we conducted such activities ourselves.

Disputes may arise regarding intellectual property subject to our current or any future license agreements, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the amount and timing of payments owed under the license agreements;
- our or our licensor's ability to defend intellectual property and to enforce intellectual property rights against third parties;
- the extent to which our technology, product candidates and processes infringe, misappropriate or otherwise violate any intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under the license agreement;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and any partners of ours; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. We are generally also subject to all of the same risks described in this Annual Report on Form 10-K with respect to protection of intellectual property that we license as we are for intellectual property that we own. If we or our licensors fail to adequately obtain or protect this intellectual property, our ability to commercialize products could suffer.

Our current and any potential future licensors might conclude that we have materially breached our license agreements and might therefore terminate the relevant license agreements, thereby removing our ability to develop and commercialize products and technology covered by such license agreements. If any of our current or future inbound license agreements are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products that are covered by such license agreements and underlying patents, which might be identical or similar to our products or product candidates. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations and growth prospects. Our business also would suffer if any current or future licensors fail to abide by the terms of the license or fail to enforce licensed patents against infringing third parties, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms. Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights.

Any licensor of ours may have relied on third-party consultants or collaborators or on funds from third parties, such as the United States government, such that such licensor is not the sole and exclusive owners of the patents we in-licensed. If other third parties have ownership rights or other rights to our in-licensed patents, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

If our efforts to protect the proprietary nature of the intellectual property related to our technologies and product candidates are not adequate, we may not be able to compete effectively in our market.

Biotechnology and pharmaceutical companies generally, and we in particular, compete in a crowded competitive space characterized by rapidly evolving technologies and aggressive development of intellectual property.

We rely upon a combination of patents, confidentiality agreements, trade secret protection and license agreements to protect the intellectual property related to our technologies and our product candidates. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate

or surpass our technological achievements and product candidates, thus eroding our competitive position in our market. We, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to strengthen our patent position.

It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we or our partners, collaborators, licensees or licensors fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees or licensors are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. We cannot be certain that the claims in any of our issued patents will be considered valid by courts in the United States or foreign countries. Third parties may challenge the validity, enforceability or scope thereof. No assurance can be given that if challenged, our patents would be declared by a court to be valid or enforceable or that even if found valid and enforceable, a competitor's technology or product would be found by a court to infringe our patents. Various post-grant review proceedings, such as inter partes review, post-grant review and derivation proceedings, are available and may be pursued by any interested third party in the USPTO to challenge the patentability of claims issued in patents to us or our licensors. No assurance can be given as to the outcome of any such post-grant review proceedings. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates or technology is threatened, it could dissuade companies from collaborating with us to develop, and threaten our ability to commercialize, our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced.

We may analyze patents or patent applications of our competitors that we believe are relevant to our activities, and consider that we are free to operate in relation to our product candidates, but our competitors may achieve issued claims, including in patents we consider to be unrelated, which block our efforts or may potentially result in our product candidates or our activities infringing such claims. On the other hand, the possibility exists that others will develop products which have the same effect as our products on an independent basis which do not infringe our patents or other intellectual property rights, or will design around the claims of patents that we have had issued that cover our products.

Recent or future patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, the Leahy-Smith America Invents Act, or America Invents Act, implemented in March 2013, moved the United States from a "first to invent" to a "first-to-file" system. Under a "first-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. The America Invents Act includes a number of other significant changes to U.S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art and establish a USPTO-administered post-grant review system that has affected patent litigation. The America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. For example:

- others may be able to make or use polypeptides or nucleic acids that are similar to our product candidates or components of our product candidates but that are not covered by the claims of our patents;

- the active biological ingredients in our current product candidates will eventually become commercially available in biosimilar drug products, and no patent protection may be available with regard to formulation or method of use;

- we or our licensors, as the case may be, may fail to meet our obligations to the U.S. government in regards to any patents and patent applications funded by U.S. government grants, leading to the loss of patent rights;

- we or our licensors, as the case may be, might not have been the first to file patent applications for these inventions;

- others may independently develop similar or alternative technologies or duplicate any of our technologies;

- it is possible that our pending patent applications will not result in issued patents;

- it is possible that there are prior public disclosures that could invalidate our or our licensors' patents, as the case may be, or parts of our or their patents;

- it is possible that others may circumvent our owned or in-licensed patents;

- it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our products or technology similar to ours;

- the laws of foreign countries may not protect our or our licensors', as the case may be, proprietary rights to the same extent as the laws of the United States;

- the claims of our owned or in-licensed issued patents or patent applications, if and when issued, may not cover our product candidates or technology;

- our owned or in-licensed issued patents may not provide us with any competitive advantages, may be narrowed in scope, or be held invalid or unenforceable as a result of legal challenges by third parties;

- the inventors of our owned or in-licensed patents or patent applications may become involved with competitors, develop products or processes which design around our patents, or become hostile to us or the patents or patent applications on which they are named as inventors;

- it is possible that our owned or in-licensed patents or patent applications omit individual(s) that should be listed as inventor(s) or include individual(s) that should not be listed as inventor(s), which may cause these patents or patents issuing from these patent applications to be held invalid or unenforceable;

- we have engaged in scientific collaborations in the past and will continue to do so in the future, and such collaborators may develop adjacent or competing products to ours that are outside the scope of our patents;

- we may not develop additional proprietary technologies for which we can obtain patent protection;

- it is possible that product candidates or technology we develop may be covered by third parties' patents or other exclusive rights; or

- the patents of others may have an adverse effect on our business.

Our proprietary position depends upon patents that are manufacturing, formulation or method-of-use patents, which may not prevent a competitor or other third party from designing around or using the same product candidate for another use.

Composition of matter patents for biological and pharmaceutical products are generally considered to be the strongest form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of making or method of use. We cannot be certain, however, that the claims in our pending patent applications, including those claims covering the composition of matter of our product candidates, will be considered patentable by the USPTO or by patent offices in foreign countries, or that the claims in any of our patents that have issued or may issue will be considered valid and enforceable by courts in the United States or foreign countries. Furthermore, in some cases, we may not be able to obtain issued claims covering compositions of matter relating to our product candidates, and instead may need to rely on secondary intellectual property, including patents or patent applications with claims covering formulations, methods of use and/or methods of manufacture. Method of use patents protect a specified method of using a product, such as a method of treating a particular medical indication. This type of patent may only be enforced against a competitor through indirect infringement, i.e., inducement or contributory infringement, which is more difficult to prove than direct infringement. A competitor may be able to circumvent this type of patent by skinny labelling. Furthermore, this type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their products for our targeted indications, physicians may prescribe these products "off-label" for those uses that are covered by our method of use patents. Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent by enforcing patent rights or otherwise.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to the protection afforded by patents, we seek to rely on trade secret protection, confidentiality agreements, and license and other agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our product discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. For example, significant elements of our product candidates, including aspects of sample preparation, methods of manufacturing, cell culturing conditions and related processes are based on unpatented trade secrets that are not publicly disclosed. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual or entity during the course of the party's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary technology by third parties. We have also adopted policies and conduct training that provides guidance on our expectations, and our advice for best practices, in protecting our trade secrets. However, we cannot provide assurance that these agreements and policies will not be breached by our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors and that our trade secrets and other proprietary and confidential information will not be disclosed to publicly or to competitors. We cannot be certain that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques.

Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our trade secrets and other confidential proprietary know-how, information, or technology both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our trade secrets and other confidential information to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results and financial condition.

If we choose to go to court to stop a third party from using any of our trade secrets, we may incur substantial costs. These lawsuits may consume our time and other resources even if we are successful.

Third-party claims of intellectual property infringement or violations may prevent or delay our discovery and development efforts.

Our commercial success depends in part on our avoiding infringement of the patents and violation of other proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, reexamination, and post-grant review proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. We may be exposed to, or threatened with, future litigation or other adversarial proceedings by third parties having patent or other intellectual property rights alleging that our product candidates and/or proprietary technologies infringe their intellectual property rights. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others. Moreover, it is not always clear to industry participants, including us, which patents may ultimately issue because many patent filings cover various types of drugs, products or their methods of use or manufacture. Thus, because of the large number of patents issued and patent applications filed in our fields, there may be a risk that third parties may allege they have patent rights encompassing our product candidates, technologies or methods.

If a third party claims that we infringe its intellectual property rights, we may face a number of issues, including, but not limited to:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business;

- substantial damages for infringement, which we may have to pay if a court decides that the product candidate or technology at issue infringes on or violates the third party's rights, and, if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner's attorneys' fees;

- a court prohibiting us from developing, manufacturing, marketing or selling our product candidates, or from using our proprietary technologies, unless the third party licenses its product rights to us, which it is not required to do;

- if a license is available from a third party, we may have to pay substantial royalties, upfront fees and other amounts, and/or grant cross-licenses to intellectual property rights for our products; and

- redesigning our product candidates or processes so they do not infringe third party intellectual property rights, which may not be possible or may require substantial monetary expenditures and time.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations or could otherwise have a material adverse effect on our business, results of operations, financial condition and prospects.

Third parties may assert that we are employing their proprietary technology without authorization. Generally, conducting preclinical and clinical trials and other development activities in the United States is not considered an act of infringement. If any of our product candidates is approved by the FDA, a third party may then seek to enforce its patent by filing a patent infringement lawsuit against us. While we do not believe that any claims that could otherwise have a materially adverse effect on the commercialization of our product candidates are valid and enforceable, we may be incorrect in this belief, or we may not be able to prove it in litigation. In this regard, patents issued in the United States by law enjoy a presumption of validity that can be rebutted only with evidence that is "clear and convincing," a heightened standard of proof. There may be issued third-party patents of which we are currently unaware with claims to compositions, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Patent applications can take many years to issue.

We cannot guarantee that any of our patent searches or analyses, including the identification of relevant patents or patent applications, the scope of pending or issued patent claims, or the expiration of relevant patents are complete, nor can we be certain that we have identified each and every third-party patent and pending application in the United States and abroad that is relevant to or necessary to commercialization of our product candidates in any jurisdiction. There may be currently

pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Moreover, we may fail to identify relevant third-party patents or incorrectly interpret the relevance, scope, or expiration of a third-party patent or incorrectly conclude that a patent is invalid, not enforceable, exhausted, or not infringed by our activities. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of our product candidates, constructs or molecules used in or formed during the manufacturing process, or any final product itself, the holders of any such patents may be able to block our ability to commercialize the product candidate unless we obtained a license under the applicable patents, or until such patents expire or they are finally determined to be held invalid or unenforceable. Similarly, if any third-party patent were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy or patient selection methods, the holders of any such patent may be able to block our ability to develop and commercialize the product candidate unless we obtained a license or until such patent expires or is finally determined to be held invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, or at all, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business. Even if we obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Parties making claims against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defense of these claims, regardless of their merit, could involve substantial litigation expense and would be a substantial diversion of resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. We cannot predict whether any such license would be available on commercially reasonable terms or at all. Furthermore, even in the absence of litigation, we may need or may choose to obtain licenses from third parties to advance our research or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly.

We may not be successful in obtaining or maintaining necessary rights to product components and processes for our development pipeline through acquisitions and in-licenses.

Currently, we have certain intellectual property rights under patents and patent applications that we own or have rights to under our inbound license agreements related to our product candidates. Our development of additional product candidates may require the use of proprietary rights held by third parties, and the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights.

Our product candidates may also require specific formulations to work effectively and efficiently, and rights to such formulation technology may be held by others. Similarly, efficient production or delivery of our product candidates may also require specific compositions or methods, and the rights to these may be owned by third parties. Moreover, the specific components, such as linkers and antibody fragments, that will be used with our product candidates may be covered by the intellectual property rights of others. We may be unable to acquire or in-license any compositions, methods of use, formulations, processes or other third-party intellectual property rights from third parties that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology.

Additionally, we may collaborate with or sponsor research at academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration or sponsorship. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

The licensing and acquisition of third-party intellectual property rights is a competitive area, and companies, which may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file lawsuits with infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that one or more of our patents is not valid or is unenforceable or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure.

Third parties may initiate post-grant proceedings and the Patent Trial and Appeal Board of the USPTO may institute such proceedings to determine the validity or priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, or at all. Litigation or post-grant proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, infringement of our patents or misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We generally enter into confidentiality and intellectual property assignment agreements with our employees, consultants, and contractors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, those agreements may not be honored and may not effectively assign intellectual property rights to us. Moreover, there may be some circumstances, where we are unable to negotiate for such ownership rights. Disputes regarding ownership or inventorship of intellectual property can also arise in other contexts, such as collaborations and sponsored research. If we are subject to a dispute challenging our rights in or to patents

or other intellectual property, such a dispute could be expensive and time consuming. If we were unsuccessful, we could lose valuable rights in intellectual property that we regard as our own.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed confidential information of our competitors or are in breach of non-competition or non-solicitation agreements with our competitors.

Many of our employees, consultants and advisers were previously employed at other pharmaceutical companies, including our competitors or potential competitors, in some cases until recently. Some of these employees, consultants, advisers, and members of management executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. Although we take steps to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants, advisers, and members of management have inadvertently or otherwise used or disclosed trade secrets or other confidential information of these former employers or competitors. In addition, we may in the future be subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our defense to those claims fails, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Any litigation or the threat thereof may adversely affect our ability to hire employees. A loss of key personnel or their work product could hamper or prevent our ability to commercialize product candidates, which could have an adverse effect on our business, results of operations and financial condition.

In the future, we may in-license intellectual property that may have been discovered through government funded programs and thus may be subject to federal regulations 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.

Any of the intellectual property rights that we have licensed or may license in the future and that have been generated through the use of U.S. government funding are subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our product candidates pursuant to the Bayh-Dole Act of 1980, or the 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, generally referred to as "march-in rights." To our knowledge, none of our current product candidates are subject to march-in rights. However, intellectual property rights that we license in the future could be subject to such limitations. The U.S. government also has the right to take title to such intellectual property rights 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. We cannot be certain that our current or future licensors will comply with the disclosure or reporting requirements of the Bayh-Dole Act at all times or be able to rectify any lapse in compliance with these requirements.

In addition, the U.S. government requires that any products embodying the subject invention or produced using 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.

If we do not obtain patent term extension for any of our current or future product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any of our current or future 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, or the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended for each marketing approval and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed.

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

Our trademarks or trade names may be challenged, infringed, circumvented, declared generic or determined to be infringing on other marks. We rely on both registration and common law protection for our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During the trademark registration process, we may receive Office Actions from the USPTO objecting to the registration of our trademark. Although we would be given an opportunity to respond to those objections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and/or to seek the cancellation of registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

The degree of future protection afforded by our intellectual property rights, whether owned or in-licensed, is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to fully exercise or extract value from our intellectual property rights. The factors that may limit any potential competitive advantage provided by our intellectual property rights include:

- pending patent applications that we own or license may not lead to issued patents;
- patents, should they issue, that we own or license, may not provide us with any competitive advantages, or may be challenged and held invalid or unenforceable;
- others may be able to develop and/or practice technology that is similar to our technology or aspects of our technology but that is not covered by the claims of any of our owned or in-licensed patents, should any such patents issue;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;
- we (or our licensors) might not have been the first to make the inventions covered by a pending patent application that we own or license;

- we (or our licensors) might not have been the first to file patent applications covering a particular invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- we may not be able to obtain and/or maintain necessary licenses on reasonable terms or at all;
- third parties may assert an ownership interest in our intellectual property and, if successful, such disputes may preclude us from exercising exclusive rights, or any rights at all, over that intellectual property;
- we may not be able to maintain the confidentiality of our trade secrets or other proprietary information;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business and results of operation.

Risks Related to Regulatory Approval and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of drug and biologic products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We are not permitted to market our product candidates in the United States or in other countries until we receive approval of an NDA or BLA from the FDA or marketing approval from applicable regulatory authorities outside the United States. Our product candidates are in various stages of development and are subject to the risks of failure inherent in development. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction. We have no experience as a company 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.

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. The FDA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Accordingly, any delay in obtaining or failure to obtain required approvals could negatively affect our ability or that of any future collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Disruptions in the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed or commercialized in a timely manner, 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 and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies 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 drugs to be reviewed or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical 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.

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

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.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad. Any approval we may be granted for our product candidates in the United States would not assure approval of our product candidates in foreign jurisdictions and any of our product candidates that may be approved for marketing in a foreign jurisdiction will be subject to risks associated with foreign operations.

In order to market and sell our products in the EU and other foreign jurisdictions, we 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 marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. We 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 file for marketing approvals but not receive necessary approvals to commercialize our products in any market.

In many countries outside the United States, a product candidate must also be approved for reimbursement before it can be sold in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. Obtaining non-U.S. regulatory approvals and compliance with non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries. In addition, if we fail to obtain the non-U.S. approvals required to market our product candidates outside the United States or if we fail to comply with applicable non-U.S. regulatory requirements, our target markets will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects may be adversely affected.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the EU on January 31, 2020 and a transition period to December 31, 2020, was established to allow the United Kingdom and the EU to negotiate the United Kingdom's withdrawal. As a result, effective January 1, 2021, the United Kingdom is no longer part of the European Single Market and European Union Customs Union. A co-operation agreement was signed between the United Kingdom and the EU in December 2020, which was applied provisionally beginning on January 1, 2021 and entered into force on May 1, 2021. The agreement addresses trade, economic arrangements, law enforcement, judicial cooperation and a governance framework including procedures for dispute resolution, among other things. As both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal.

The U.K.'s withdrawal from the EU took place on January 31, 2020. The EU and the U.K. reached an agreement on their new partnership in the Trade and Cooperation Agreement, or the TC Agreement, which was applied provisionally beginning on January 1, 2021 and which entered into force on May 1, 2021. The TC 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 U.K. will form two separate markets governed by two distinct regulatory and legal regimes. As such, the TC Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the U.K. 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 U.K.'s withdrawal from the EU.

Since a significant proportion of the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the U.K. For example, the U.K. is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the U.K. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure.

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 not be able to obtain orphan drug designation or orphan drug exclusivity for our product candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing products.

Regulatory authorities in some jurisdictions, including the United States and the EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States. Generally, a product with orphan drug designation only becomes entitled to orphan drug exclusivity if it receives the first marketing approval for the indication for which it has such designation, in which case the FDA or the EMA will be precluded from approving another marketing application for the same product for that indication for the applicable exclusivity period. The applicable exclusivity period is seven years in the United States and ten years in the EU. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified.

We may seek orphan drug designations for our product candidates and may be unable to obtain such designations. Even if we do secure such designations and 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. Further, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, to be more effective or to make a major contribution to patient care. Finally, orphan drug exclusivity may be lost if the FDA or the 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 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." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

Any product candidate for which we obtain marketing approval is subject to ongoing regulation and 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, when and if any of our product candidates are approved.

Any product candidate for which we obtain marketing approval 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, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. In addition, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy. Accordingly, if we receive marketing approval for one or more of our product candidates, we will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we fail to comply with these requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any products could be limited, which could adversely affect our ability to achieve or sustain profitability.

We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription products are subject to a variety

of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. The FDA and other agencies, including the Department of Justice closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. 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 drug or biologic. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

Failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on distribution or use of a product;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- damage to relationships with collaborators;
- unfavorable press coverage and damage to our reputation;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our products.

Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the EU's requirements regarding the protection of personal information can also lead to significant penalties and sanctions. Further, the marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and are also subject to EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

We may seek certain designations for our product candidates, including Breakthrough Therapy, Fast Track and Priority Review designations in the United States and PRIME Designation in the EU, but we might not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process.

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious 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. For products that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens.

The FDA may also designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective.

We may also seek a priority review designation for one or more of our product candidates. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months.

These designations are within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. Further, even if we receive a designation, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualifies for these designations, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

In the EU, we may seek PRIME designation for some of our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU and the applicant intends to apply for an initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims. The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

Current and future legislation may increase the difficulty and cost for us to obtain reimbursement for any of our candidate products that do receive marketing approval.

In the United States and 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 product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. We expect that 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 may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In addition, other legislative changes have been proposed and adopted since the ACA 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 CARES Act. Pursuant to subsequent legislation, however, these Medicare sequester reductions were reduced and suspended through the end of June 2022, with the full 2% cut resuming thereafter. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Under current legislation, the actual reductions in Medicare payments may vary up to 4%.

Since enactment of the ACA, 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, which was signed by President Trump on December 22, 2017, 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 ACA is an essential and inseverable feature of the ACA and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA 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 ACA. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA 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 an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how such other challenges to repeal or replace the ACA or the health reform measures of the Biden administration will impact the ACA or our business.

Current and future legislative efforts may limit the prices for our products, if and when they are licensed for marketing, and that could materially impact our ability to generate revenues.

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 until January 1, 2026 by the Infrastructure Investment and Jobs Act. The final rule would eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with the passage of the Inflation Reduction Act has been delayed by Congress to January 1, 2032.

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

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

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been

licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or "catastrophic period" of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

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

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare 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 healthcare 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 product candidates or additional pricing pressures.

Finally, outside the United States, in some nations, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. 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 or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product 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 materially harmed.

We may be subject to certain healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished future profits and earnings, if any.

Healthcare providers, third-party payors and others will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our current and future arrangements with healthcare providers and third-party payors will 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 research as well as market, sell and

distribute any products for which we obtain marketing approval. Potentially applicable U.S. federal and state healthcare laws and regulations include the following:

- *Anti-Kickback Statute*. The federal Anti-Kickback Statute prohibits, among other things, persons and entities 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 healthcare programs such as Medicare and Medicaid.

- *False Claims Laws*. The federal false claims laws and civil monetary penalties laws, including the civil False Claims Act and the Civil Monetary Penalty Law, impose criminal and civil penalties, including those from 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 that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government.

- *HIPAA*. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program.

- *HIPAA and HITECH*. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or the HITECH Act, also imposes obligations on certain types of individuals and entities, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

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

- *Transparency Requirements.* The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the Department of Health and Human Services information related to payments and other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors), other healthcare providers, and ownership and investment interests by physicians and their immediate family members. As of January 1, 2022, applicable manufacturers are also required to report such information regarding its payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives during the previous year.

- *Analogous State and Foreign Laws*. Analogous state laws and regulations, such as state anti-kickback and false claims laws, and transparency laws, 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 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 manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. Many state 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. Foreign laws also govern the privacy and security of health information in many circumstances.

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 EU. Payments made to physicians in certain EU 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 EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct applicable in the EU 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, and our business generally, 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, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, and reputational harm, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, contractual obligations and 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.

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the U.S., EU and U.K. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether protected health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

In 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or the GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to

opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Similar to the laws in the U.S., there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or the EEA, and the processing of personal data that takes place in the EEA, is regulated by the GDPR, which went into effect in May 2018 and which imposes obligations on companies that operate in our industry with respect to the processing of personal data and the cross-border transfer of such data. The GDPR imposes onerous accountability obligations requiring data controllers and processors to maintain a record of their data processing and policies. If our or our partners' or service providers' privacy or data security measures fail to comply with the GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

The GDPR places restrictions on the cross-border transfer of personal data from the EU to countries that have not been found by the EC to offer adequate data protection legislation, such as the U.S. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U.S. While we were not self-certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EEA to the U.S. generally and increase our costs of compliance with data privacy legislation, as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-US Privacy Shield. The European Commission, or the EC, initiated the process to adopt an adequacy decision for the EU-US Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the U.K. and the EU have determined, through separate "adequacy" decisions, that data transfers between the two jurisdictions are in compliance with the U.K. Data Protection Act and the GDPR, respectively. Any changes or updates to these adequacy decisions have the potential to impact our business.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and the sale and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the U.S. regarding privacy and security of personal information could expose us to penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. 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 business, financial condition, results of operations or prospects.

We are subject to U.S. and certain foreign export control, import, sanctions, anti-corruption, and anti-money laundering laws and regulations with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 202, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. In addition, we may engage third-party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Noncompliance with the laws and regulations described above could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage and other collateral consequences. If any subpoenas, investigations or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

Changes in U.S. and international trade policies, particularly with respect to China, may adversely impact our business and operating results.

The U.S. government has recently made statements and taken certain actions that may lead to potential changes to U.S. and international trade policies, including imposing several rounds of tariffs and export control restrictions affecting certain products manufactured in China. In March 2018, the Trump administration announced the imposition of tariffs on steel and aluminum entering the United States and in June 2018 announced further tariffs targeting goods imported from China. Recently both China and the United States have each imposed tariffs indicating the potential for further trade barriers, including the U.S. Commerce Department adding numerous Chinese entities to its "unverified list," which requires U.S. exporters to go through more procedures before exporting goods to such entities. It is unknown whether and to what extent

new tariffs, export controls, or other new laws or regulations will be adopted, or the effect that any such actions would have on us or our industry, and it is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. While we have not started commercialization of drug candidates, any unfavorable government policies on international trade, such as export controls, capital controls or tariffs, may affect the demand for our drug products, the competitive position of our product candidates, and import or export of raw materials and finished product candidate used in our preclinical studies and clinical trials, particularly with respect to our manufactured product candidates that we import from China, including pursuant to our manufacturing arrangements and license agreement with WuXi Biologics (Hong Kong) Limited. If any new tariffs, export controls, legislation and/or regulations are implemented, or if existing trade agreements are renegotiated or, in particular, if the U.S. government takes retaliatory trade actions due to the recent U.S.-China trade tension, such changes could have an adverse effect on our business, financial condition and results of operations.

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 harm our business.

We are subject 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. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our 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 for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, however this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

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

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, CROs, consultants, commercial partners, vendors and, if we commence clinical trials, our principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions, provide accurate information to the FDA, the 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. Even with appropriate policies and procedures, it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent such 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.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

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

We are highly dependent on the management, research and development, clinical, financial and business development expertise of our executive officers, as well as the other members of our scientific and clinical teams. Although we have employment offer letters which outline the terms of employment with each of our executive officers, each of them may terminate their employment with us at any time. As such, these employment offer letters do not guarantee our retention of our executive officers for any period of time. In addition, insurance coverage is increasingly expensive, including with respect to directors and officers' liability insurance, or D&O insurance. We may not be able to maintain D&O insurance at a reasonable cost or in an amount adequate to satisfy any liability that may arise. An inability to secure and maintain D&O insurance may make it difficult for us to retain and attract talented and skilled directors and officers to serve our company, which could adversely affect our business. We do not maintain "key person" insurance for any of our employees.

Recruiting and retaining qualified scientific and clinical personnel and, if we are successful in obtaining marketing approval for our product candidates, sales and marketing personnel, is and will be critical to our success. The loss of the services of our executive officers or other key employees could impede, delay or prevent the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval for and commercialize products in the life sciences industry, and specifically our product candidates. We are based in Massachusetts, a state that is home to many other biopharmaceutical companies as well as many academic and research institutions, resulting in fierce competition for qualified personnel. Furthermore, to the extent we hire personnel from competitors, we may be subject to allegations that they have been improperly solicited or that they have divulged proprietary or other confidential information, or that their former employers own their research output. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Additionally, the United States is experiencing a workforce shortage, which in turn has created a competitive wage environment, which is likely to further exacerbate the foregoing risks and may impact our ability to retain our executive officers or other key employees. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited and could adversely affect our business, prospects, financial condition and results of operations.

We expect to grow our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of February 15, 2023, we had 89 full-time employees. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, regulatory affairs, finance and, if any of our product candidates receive marketing approval, sales, marketing and distribution. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities to devote time to managing these growth activities. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Our inability to effectively manage the expansion of our operations may result in weaknesses in our infrastructure, and could give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant

capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our expected growth, our expenses may increase more than expected, our potential ability to generate revenue could be reduced and we may not be able to implement our business strategy.

We depend on our information technology systems and associated third-party service providers, and any failure of these systems could harm our business. Security breaches, loss of data, inability to access systems, and other disruptions could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business, results of operations and financial condition.

We collect and maintain information in digital and other forms that is necessary to conduct our business, and we are increasingly dependent on information technology systems and infrastructure to operate our business. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the privacy, security, confidentiality, availability and integrity of such confidential information. Our internal information technology systems and infrastructure, and those of our contractors, consultants, vendors, service providers and other third parties on which we rely, are vulnerable to damage or unauthorized access or use resulting from computer viruses, malware, natural disasters, terrorism, war, telecommunication and electrical failures, cyber-attacks or cyber-intrusions over the Internet, denial or degradation of service attacks, ransomware, hacking, phishing and other social engineering attacks, attachments to emails, intentional or accidental actions or inactions by persons inside our organization or by persons with access to systems inside our organization.

The risk of a security breach or disruption or data loss, particularly through cyber-attacks or cyber intrusion, including by computer hackers, supply chain attacks, 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. In addition, the prevalent use of mobile devices that access confidential information increases the risk of lost or stolen devices, security incidents and data security breaches, which could lead to the loss of confidential information or other intellectual property. We also may face increased risks of a security breach or disruption due to our reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. The costs to us to mitigate network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service, negative publicity and other harm to our business and our competitive position. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product development programs.

Any security compromise affecting us, our partners, our service providers or our industry, whether real or perceived, could harm our reputation, erode confidence in the effectiveness of our security measures and lead to regulatory scrutiny. If such an event were to occur and cause interruptions in our operations or result in the unauthorized acquisition of or access to personally identifiable information or individually identifiable health information (violating certain privacy laws, as applicable, such as HIPAA, CCPA, HITECH and GDPR), it could result in a material disruption of our discovery and development programs and our business operations, whether due to a loss of our trade secrets or other similar disruptions. Some of the federal, state and foreign government requirements include obligations of companies to notify individuals of security breaches involving particular personally identifiable information, which could result from breaches experienced by us or by our vendors, contractors, or organizations with which we have formed strategic relationships. Notifications and follow-up actions related to a security breach could impact our reputation, cause us to incur significant costs, including legal expenses and remediation costs. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the lost data. We would also be exposed to a risk of loss, governmental investigations or enforcement, or litigation and potential liability, any of which could materially adversely affect our business, results of operations and financial condition.

A variety of risks associated with marketing our product candidates internationally, if approved, could materially adversely affect our business.

We also plan to seek regulatory approval of our product candidates outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating, including conducting marketing and sales activities, in international jurisdictions if we obtain the necessary approvals, including:

- regulatory requirements in foreign countries that differ from those in the United States;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other 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 taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the FCPA or other comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism or natural disasters including pandemics or other outbreaks of infectious disease, earthquakes, typhoons, floods and fires.

Any of these factors, along with other risks associated with international operations, could materially adversely affect our future international expansion and operations and, consequently, our results of operations.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Additional potential transactions that we may consider in the future include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any future transactions could increase our near and long-term expenditures, result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could affect our financial condition, liquidity and results of operations. Future acquisitions may also require us to obtain additional capital, which may not be available on favorable terms or at all. These transactions may not be successful and may require significant time and attention of management. In addition, the integration of any business

that we may acquire in the future may disrupt our existing business and may be a complex, risky and costly endeavor for which we may never realize any or all potential benefits of the acquisition. Accordingly, although there can be no assurance that we will undertake or successfully complete any additional transactions of the nature described above, any additional transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

The impact of the COVID-19 pandemic may affect our ability to initiate and complete preclinical studies, delay the initiation of our planned and any future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations. In addition, this pandemic has caused substantial disruption in the financial markets and may adversely impact economies worldwide, each of which could result in adverse effects on our business, on raising capital and on our operations.

The COVID-19 pandemic has continued to have significant impact, both direct and indirect, on businesses and commerce, including worker shortages and supply chain disruptions. While the FDA approved emergency use authorization of vaccines in December 2020, the emergence of new variants has limited their overall efficacy. Therefore, the future progression of the outbreak and its effects on our business and operations continue to be uncertain. We and our CMOs and CROs may face disruptions in the future that affect our ability to initiate and complete preclinical studies or clinical trials, including recruitment and retention of critical employees, and disruptions or delays in completing manufacturing activities or in procuring items that are essential for our research and development activities, such as raw materials used in the manufacture of any product candidates we may develop, laboratory supplies used in our preclinical studies, or animals that are used for preclinical testing for which there are shortages because of ongoing efforts to address the outbreak. For example, in 2020, we experienced a temporary shortage of raw material used in the manufacturing process for one of our product candidates.

We may experience additional delays in the future as a result of the impacts of the COVID-19 pandemic or otherwise, which could delay our product development timelines. We and our CMOs and CROs may also face disruptions related to our future IND-enabling studies and clinical trials arising from delays in preclinical studies, manufacturing disruptions, and the ability to obtain necessary IRB, IBC or other necessary site approvals, as well as other delays at clinical trial sites. The global response to the COVID-19 pandemic may redirect resources with respect to regulatory and intellectual property matters in a way that could adversely impact our ability to progress regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions. The COVID-19 pandemic has in the past caused significant disruptions in the financial markets, and may cause such disruptions in the future, which could impact our ability to raise additional funds through the capital markets and may also impact the volatility of our stock price and trading in our stock. In addition, a recession, depression, inflation or other sustained adverse market event resulting from the COVID-19 pandemic, directly or indirectly, could materially and adversely affect our business and the value of our common stock. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business, and it has the potential to adversely affect our business, financial condition, results of operations and prospects.

Our operations or those of the third parties upon whom we depend might be affected by the occurrence of a catastrophic event, such as a terrorist attack, war or other armed conflict, geopolitical tensions or trade wars, pandemic or natural disaster.

We depend on our employees, consultants, CMOs, CROs, as well as regulatory agencies and other parties, for the continued operation of our business. While we maintain disaster recovery plans, they might not adequately protect us. Despite any precautions that we or any third parties on whom we depend take for catastrophic events, including terrorist attacks, wars or other armed conflicts, geopolitical tensions or trade wars, pandemics or natural disasters, these events could result in significant disruptions to our research and development, manufacturing, preclinical studies, clinical trials, and, ultimately, if approved, the commercialization of our products. Long-term disruptions in the infrastructure caused by these types of events, such as natural disasters, which are increasing in frequency due to the impacts of climate change, the outbreak of wars or other armed conflicts (such as Russia's invasion of Ukraine), the escalation of hostilities, geopolitical tensions or trade wars, acts of terrorism or "acts of God," particularly involving geographies in which we or third parties on whom we depend have offices, manufacturing or clinical trial sites, could adversely affect our businesses. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us

in certain events, our coverage might not include or be adequate to compensate us for all losses that may occur. Any catastrophic event affecting us, our CMOs, our CROs, regulatory agencies or other parties with which we are engaged could have a material adverse effect on our operations and financial performance.

Risks Related to Ownership of Our Common Stock and Our Status as a Public Company

An active trading market for our common stock may not continue to be developed or sustained.

Our common stock began trading on the Nasdaq Global Select Market on October 22, 2021. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares, or at all.

The price of our common stock could be subject to volatility related or unrelated to our operations and purchasers of our common stock could suffer a decline in value.

The market price of our common stock may fluctuate significantly in response to numerous factors, many of which are beyond our control. The stock market in general and the market for biotechnology and pharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- the results from our preclinical studies and clinical trials;
- the commencement, enrollment or results of any current or future clinical trials we may conduct, or changes in the development status of our product candidates;
- adverse results from, delays in initiating or completing, or termination of clinical trials;
- unanticipated serious safety concerns related to the use of our product candidates;
- clinical trial results from, or regulatory developments regarding, a competitor's product candidate;
- adverse regulatory decisions, including failure to receive regulatory approval of our product candidates;
- regulatory or legal developments in the United States and foreign countries;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- the public's response to press releases or other public announcements by us or third parties, including our filings with the Securities and Exchange Commission, and announcements relating to acquisitions, strategic transactions, licenses, joint ventures, collaborations, capital commitments, intellectual property, litigation or other disputes impacting us or our business;
- lower than expected market acceptance of our product candidates, if approved;
- adverse developments concerning our manufacturers;
- our inability to obtain adequate product supply for any approved product or inability to do so at acceptable prices;

- variations in the level of expenses related to our preclinical and clinical development programs, including relating to the timing of invoices from, and other billing practices of, our CROs and clinical trial sites;
- variations in the level of expenses related to our commercialization activities, if any product candidates are approved;
- the clinical results of our competitors or potential competitors;
- introduction of new products or services by our competitors;
- changes in financial estimates by us or by any securities analysts who might cover our common stock;
- conditions or trends in our industry;
- our cash position;
- sales of our common stock by us or our stockholders in the future;
- adoption of new, or changes to current accounting standards;
- ineffectiveness of our internal controls;
- changes in the market valuations of similar companies;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biotechnology and pharmaceutical industry;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- changes in the structure of healthcare payment systems;
- investors' general perception of our company and our business;
- overall performance of the equity markets;
- trading volume of our common stock;
- potential inclusion or exclusion of our common stock in exchange, industry, or other tracking indices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies and product candidates;
- significant lawsuits, including patent or stockholder litigation;
- proposed changes to healthcare laws, intellectual property laws or pharmaceutical pricing in the United States or foreign jurisdictions, or speculation regarding such changes;

- future sales of our common stock by our officers, directors and significant stockholders;
- recruitment or departure of key personnel;
- developments with respect to the COVID-19 pandemic;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

In addition, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

If securities or industry analysts do not publish research or reports about our company, or if they issue unfavorable or inaccurate research regarding our business, or if they publish negative evaluations of our stock, the price and trading volume of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that securities or industry analysts publish about us or our business. A limited number of securities and industry analysts currently publish research on our company. 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 covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provides more favorable relative recommendations about our competitors, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

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

General economic conditions, both inside and outside the U.S., including without limitation heightened inflation, capital market volatility, interest rate and currency rate fluctuations, any potential economic slowdown or recession, the COVID-19 pandemic (including variants of COVID-19) and geopolitical events, including trade wars or civil or political unrest (such as the ongoing war between Ukraine and Russia), have resulted in a significant disruption of global financial markets. If the disruption persists or deepens, we could experience an inability to raise additional capital. In addition, market volatility, high levels of inflation and interest rate fluctuations may increase our cost of financing or restrict our access to potential sources of future capital. For example, the prime rate has recently exceeded the interest rate floor of 4.75% under our loan and security agreement with PacWest, which has increased the amount of cash needed to service our outstanding indebtedness. Adequate additional financing may not be available to us on acceptable terms, or at all. If we are unable to raise additional capital when needed or on attractive terms, our business, financial condition, stock price and results of operations could be adversely affected, and we could be forced to delay, reduce or altogether terminate one or more current or future research and development programs. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive such difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business. Furthermore, our stock price may decline due in part to the volatility of the stock market and any general economic downturn.

Our principal stockholders and management own a significant percentage of our common stock and exert significant control over matters subject to stockholder approval.

As of February 15, 2023, our executive officers, directors, holders of 5% or more of our common stock and their respective affiliates beneficially owned shares in the aggregate representing a majority of our outstanding common stock. As a result of their share ownership, these stockholders, if they act together, would have the ability to influence our management and policies and would be able to significantly affect the outcome of matters requiring stockholder approval such as elections of directors, amendments of our organizational documents or approvals of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that our stockholders may feel are in their best interest.

Some of these persons or entities may have interests different than our unaffiliated stockholders. For example, because many of these stockholders purchased their shares at prices substantially below the current market price and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other stockholders. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

- delaying, deferring or preventing a change of control of us;
- entrench our management and board of directors;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

We have broad discretion regarding use of our cash and cash equivalents, and we may not use them effectively.

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

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any determination to pay dividends in the future will be at the sole discretion of our board of directors. In addition, the terms of any future debt agreements may preclude us from paying dividends. Any return to stockholders will therefore be limited in the foreseeable future to the appreciation of their stock.

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 Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an EGC until December 31, 2026, although if the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have annual gross revenues of $1.235 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1.0 billion of non-convertible debt over a three-year period. 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:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of financial Condition and Results of Operations" disclosure;

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;

- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

- reduced disclosure obligations regarding executive compensation; and

- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

Even after we no longer qualify as an emerging growth company, we may continue to qualify as a smaller reporting company, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including reduced disclosure obligations regarding executive compensation. In addition, if we are a smaller reporting company with less than $100 million in annual revenue, we would not be required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404.

We cannot predict whether investors will find our common stock less attractive if we rely 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.

In addition, the JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we can adopt the new or revised standard at the time private companies adopt the new or revised standard and may do so until such time that we either (1) irrevocably elect to "opt out" of such extended transition period or (2) no longer qualify as an EGC or a smaller reporting company. We may choose to early adopt any new or revised accounting standards whenever such early adoption is permitted for private companies.

We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management has devoted and will continue to be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, Nasdaq listing requirements, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements and will make some activities more time-consuming and costly.

We are evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If notwithstanding our efforts to comply with new laws, regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be materially adversely effected.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an EGC or a smaller reporting company with less than $100 million in annual revenue, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To comply with Section 404, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also subject us to regulatory scrutiny and sanctions, impair our ability to raise revenue and cause investors to lose confidence in our reported financial information, which could harm our business and have a negative effect on the trading price of our common stock and adversely affect our results of operations and financial condition.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an EGC or a smaller reporting company with less than $100 million in annual revenue, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404. We could be an emerging growth company for up to five years. An independent assessment of the effectiveness of our internal control over financial reporting could detect problems that our management's assessment might not. Undetected material weaknesses in our internal control over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation, which could have a negative effect on the trading price of our common stock and adversely affect our results of operations and financial condition.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

As a public company, we are subject to certain reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to

management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal control over financial reporting, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. The Tax Act, enacted on December 22, 2017, as amended by the CARES Act, enacted on March 27, 2020, contained significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for NOLs arising in taxable years beginning after December 31, 2017 to 80% of current-year taxable income (though such NOLs may be carried forward indefinitely) and elimination of the carryback for NOLs arising in taxable years beginning after December 31, 2020, the imposition of a one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time, and the modification or repeal of many business deductions and credits. In addition to the CARES Act, as part of Congress's response to the COVID-19 pandemic, additional legislation has been enacted in 2020 and 2021 containing tax provisions. Regulatory guidance under the Tax Act, CARES Act, and such additional legislation is and continues to be forthcoming. Such guidance could ultimately increase or lessen the impact of these laws on our business and financial condition. Congress may enact additional legislation in connection with the COVID-19 pandemic, and as a result of changes in the U.S. presidential administration and control of the U.S. Senate, additional tax legislation may also be enacted, which could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the CARES Act, and additional tax legislation.

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

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

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;

- limit who may call stockholder meetings;

- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and

- require the approval of the holders of at least two-thirds of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

In addition, these provisions would apply even if we were to receive an offer that some stockholders may consider beneficial. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or the DGCL, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Our restated certificate of incorporation designates the Court of Chancery of the State of Delaware and the federal district courts of the United States of America as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers and employees and increase the costs to our stockholders of bringing such claims.

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;

- any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders;

- any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware; or

- any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine.

These choice of forum provisions will not apply to suits brought to enforce a duty or liability created by the Exchange Act. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions, and investors cannot waive compliance with the federal securities laws and the rules and regulations thereunder. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our restated certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

These exclusive forum provisions may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, and increase the costs to such stockholders of bringing such a claim, either of which may discourage such lawsuits against us and our directors, officers and employees. If a court were to find the either exclusive forum provision contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving such action in other jurisdictions, all of which could materially adversely affect our business, financial condition and operating results.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We occupy approximately 28,000 square feet of office and laboratory space in Waltham, Massachusetts under a lease that expires in March 2030 with an option to renew for an additional five years. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are currently not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock is traded on the Nasdaq Global Select Market under the symbol "XLO". Trading of our common stock commenced on October 22, 2021, following the completion of our initial public offering, or IPO. Prior to that date, there was no public market for our common stock.

Holders

As of February 15, 2023, there were 58 holders of record of our common stock. This number does not include beneficial owners whose shares are held in street name.

Dividend Policy

We have never paid cash dividends and we do not anticipate paying any cash dividends on our shares of common stock in the foreseeable future. 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.

Use of Proceeds from Initial Public Offering of Common Stock

On October 26, 2021, we closed our IPO and issued and sold an aggregate of 7,353,000 shares of our common stock at a public offering price of $16.00 per share, and on November 1, 2021, we sold an additional 766,106 shares of common stock at a public offering price of $16.00 per share pursuant to the partial exercise by the underwriters of their option to purchase additional shares.

The offer and sale of the shares of common stock in our IPO was registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-259973), which was declared effective by the SEC on October 21, 2021. Following the sale of the shares in connection with the partial exercise by the underwriters of their option, the offering terminated before all the securities registered in the registration statement were sold. Morgan Stanley & Co. LLC, Cowen and Company LLC and Guggenheim Securities, LLC acted as joint book-running managers for our IPO, and Raymond James & Associates, Inc. acted as lead manager for our IPO.

We received aggregate gross proceeds from our IPO, inclusive of the exercise by the underwriters of their option to purchase additional shares, of $129.9 million, or aggregate net proceeds of $116.4 million, after deducting underwriting discounts and commissions and offering expenses payable by us. None of these expenses consisted of direct or indirect payments made by us to directors, officers or persons owning 10% or more of our common stock or to their associates, or to our affiliates.

As of December 31, 2022, we estimate that we have used approximately $95.0 million of the net proceeds from our IPO. We maintain the unused net proceeds from the offering in cash and cash equivalents. In November 2022, we announced that we plan to continue to explore opportunities for strategic collaborations to advance XTX101 and that we do not plan to initiate an anti-PD-1/PD-L1 combination cohort in the Phase 1 clinical trial or initiate a Phase 2 clinical trial for XTX101 without a partner. Other than the foregoing, there has been no material change in the planned use of the net proceeds from our IPO, as described in our final prospectus filed with the SEC on October 22, 2021 pursuant to Rule 424(b)(4) under the Securities Act.

Item 6. [Reserved]

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

The following discussion and analysis is meant to provide material information relevant to an assessment of the financial condition and results of operations of our company, including an evaluation of the amounts and uncertainties of cash flows from operations and from outside resources, so as to allow investors to better view our company from management's perspective. You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K.

Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the section entitled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. You should carefully read the section entitled "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K to gain an understanding of the important factors that could cause actual results to differ materially from our forward-looking statements.

Overview

We are a clinical-stage biotechnology company discovering and developing tumor-activated immuno-oncology, or I-O, therapies with the goal of significantly improving outcomes for people living with cancer without the systemic side effects of current I-O treatments. We are leveraging our proprietary geographically precise solutions, or GPS, platform to build a pipeline of novel, tumor-activated molecules, including cytokines and other biologics, which are designed to optimize their therapeutic index by localizing anti-tumor activity within the tumor microenvironment. Current I-O therapies have

curative potential for patients with cancer; however, their potential is significantly curtailed by systemic toxicity that results from activity of the therapeutic molecule outside the tumor microenvironment. Our molecules are engineered to localize activity within the tumor microenvironment with minimal systemic effects, resulting in the potential to achieve enhanced anti-tumor activity and increasing the population of patients who may be eligible to receive our medicines. Our most advanced tumor-activated, clinical-stage product candidates are XTX202, an interleukin 2, or IL-2, therapy, XTX301, an interleukin 12, or IL-12, therapy and XTX101, an Fc-enhanced, anti-CTLA-4 monoclonal antibody, or mAb. In addition to our clinical-stage product candidates, we are continuing to leverage our GPS platform and expertise in developing tumor-activated I-O therapies as we seek to expand our pipeline of discovery-stage programs and develop additional tumor-activated immunotherapies, including product candidates with a range of tumor targeting approaches.

To date, we have financed our operations primarily from proceeds raised through private placements of preferred units and convertible preferred stock, a debt financing and our initial public offering, or IPO, of common stock in October 2021. Through December 31, 2022, we have received an aggregate of $350.9 million in net proceeds from such transactions, including aggregate net proceeds of $116.4 million from our IPO, an aggregate of $224.5 million in net proceeds from the sale and issuance of preferred units and convertible preferred stock, and $10.0 million in net proceeds from our debt financing with Pacific Western Bank, or PacWest.

We are party to a sales agreement with Cowen and Company LLC, or Cowen, under which we may issue and sell shares of our common stock, from time to time, having an aggregate offering price of up to $75.0 million, subject to the terms and conditions of the sales agreement. As of December 31, 2022, we have not issued or sold any of our common stock pursuant to the sales agreement and $75.0 million of shares of common stock remain available to be sold pursuant to the sales agreement, which sales, if any, would be made under our universal shelf registration statement on Form S-3, or the 2022 Shelf.

We have not generated any revenue from product sales, and do not expect to generate any revenue from product sales for at least the next several years, if at all. All of our programs are in early clinical or preclinical development. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of one or more of our product candidates, if approved. Since inception, we have incurred significant operating losses, including net losses of $88.2 million and $75.8 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $249.1 million. We expect to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will continue to increase significantly in connection with our ongoing activities, particularly as we:

- continue to advance our current research programs and conduct additional research programs;
- advance our current product candidates and any future product candidates we may develop into preclinical and clinical development;
- seek marketing approvals for product candidates that successfully complete clinical trials, if any;
- obtain, expand, maintain, defend and enforce our intellectual property;
- hire additional research, clinical, regulatory, quality, manufacturing and general and administrative personnel;
- establish a commercial and distribution infrastructure to commercialize products for which we may obtain marketing approval, if any;
- continue to discover, validate and develop additional product candidates;
- continue to manufacture increasing quantities of our current or future product candidates for use in preclinical studies, clinical trials and for any potential commercialization;
- acquire or in-license other product candidates, technologies or intellectual property; and

- incur additional costs associated with current and future research, development and commercialization efforts and operations as a public company.

As a result, we will need substantial additional capital to support our continuing operations and pursue our strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings and other sources of funding, such as collaborations, licensing arrangements or other strategic transactions. We may be unable to raise additional capital or enter into such other agreements or arrangements when needed on acceptable terms, or at all. Our failure to raise capital or enter into such agreements as and when needed could have a material adverse effect on our business, results of operations and financial condition.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2022, we had cash and cash equivalents of $120.4 million. We believe that our existing cash and cash equivalents will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2024.

Note Regarding the COVID-19 Pandemic

The impact of the COVID-19 pandemic continues to be widespread, rapidly-evolving and unpredictable on global societies, economies, financial markets, supply chains and business practices. The extent of the impact of the COVID-19 pandemic, including variants of the COVID-19 virus, on our business, operations, and clinical development timelines and plans remains uncertain. For a discussion regarding risks and uncertainties related to the impact of the COVID-19 pandemic and its potential impact on our business and financial results, please refer to our "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K.

Financial Operations Overview

Revenue

We have not generated any revenue since inception and do not expect to generate any revenue from the sale of products for at least the next several years, if at all. If our development efforts for our current or future product candidates are successful and result in regulatory approval or if we enter into collaboration or license agreements with third parties, we may generate revenue in the future from product sales or payments from third-party collaborators or licensors.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our discovery efforts, research activities and development and testing of our programs and product candidates. These expenses include:

- personnel-related expenses, including salaries, bonuses, benefits and equity-based compensation expense for employees engaged in research and development functions;

- costs incurred with third-party contract development and manufacturing organizations, or CDMOs, to acquire, develop and manufacture materials for both preclinical studies and current or future clinical trials;

- costs of funding research performed by third parties that conduct research and development and preclinical activities on our behalf;

- costs incurred with third-party contract research organizations, or CROs, and other third parties in connection with the conduct of our current or future clinical trials;

- costs of sponsored research agreements and outside consultants, including their fees, equity-based compensation and related expenses;

- costs incurred to maintain compliance with regulatory requirements;

- fees for maintaining licenses and other amounts due under our third-party licensing agreements;

- expenses incurred for the procurement of materials, laboratory supplies and non-capital equipment used in the research and development process; and

- depreciation, amortization and other direct and allocated expenses, including rent, insurance, maintenance of facilities and other operating costs, incurred as a result of our research and development activities.

We expense research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific deliverables using information provided to us by our vendors. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid expenses or accrued research and development expenses. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are capitalized as assets, even when there is no alternative future use for the research and development. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

We use our personnel and infrastructure resources for our discovery efforts, including the advancement of our GPS platform, developing programs and product candidates and managing external research efforts. A significant portion of our research and development costs have been, and will continue to be, external costs. We track these external costs, such as fees paid to CDMOs, CROs, preclinical study vendors and other third parties in connection with our manufacturing and manufacturing process development, clinical trials, preclinical studies and other research activities by program. Due to the number of ongoing programs and our ability to use resources across several projects, personnel-related expenses and indirect or shared operating costs incurred for our research and development programs are not recorded or maintained on a program-by-program basis.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as we advance our programs and product candidates into and through clinical development, and as we continue to develop additional product candidates. We also expect our discovery research efforts and our related personnel costs will continue to increase and, as a result, we expect our research and development expenses, including costs associated with equity-based compensation, will continue to increase above historical levels. In addition, we may incur additional expenses related to milestone and royalty payments payable to third parties with whom we have entered into, or may enter into license, acquisition, option or other agreements to acquire the rights to future products and product candidates.

At this time, we cannot reasonably estimate or know the nature, timing and projected costs of the efforts that will be necessary to complete the development of, and obtain regulatory approval for, any of our product candidates or programs. This is due to the numerous risks and uncertainties associated with drug development, including the uncertainty of:

- the scope, timing, costs and progress of preclinical and clinical development activities;

- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to maintain our current research and development programs and to establish new ones;
- our ability to establish an appropriate safety profile for our product candidates with IND-enabling studies;
- our ability to hire and retain key research and development personnel;
- the costs associated with the development of any additional product candidates we develop or acquire through collaborations;
- our successful enrollment in and completion of clinical trials;
- our ability to successfully complete clinical trials with safety, potency and purity profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- our receipt of regulatory approvals from applicable regulatory authorities;
- our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize, our product candidates;
- our ability to commercialize products, if and when approved, whether alone or in collaboration with others;
- the continued acceptable safety profiles of the product candidates following approval, if any;
- our ability to establish and maintain agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if any of our product candidates are approved;
- the terms and timing of any collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder, if any;
- our ability to obtain and maintain patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates if and when approved;
- general economic conditions, including inflation; and
- the impact of public health crises, including epidemics and pandemics such as the COVID-19 pandemic, on our business, operations, strategy, goals and anticipated milestones, as well as our response to such epidemics or pandemics.

A change in any of these variables with respect to the development of any of our product candidates would significantly change the costs, timing and viability associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any product candidate we may develop.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related costs, including salaries, bonuses, benefits, recruiting and equity-based compensation, for personnel in our executive, finance, legal, business development, human resources and other administrative functions. General and administrative expenses also include legal fees relating to corporate matters; professional and consulting fees for accounting, auditing, tax, human resources and administrative consulting services; insurance costs; and facility-related expenses, which include depreciation costs and other allocated expenses for rent, maintenance of facilities, and other general administrative costs. These costs relate to the operation of

the business and are in support of but separate from the research and development function and our individual development programs. Costs to secure and defend our intellectual property are expensed as incurred and are classified as general and administrative expenses.

We anticipate that our general and administrative expenses will increase in the future as we increase infrastructure to support the expected growth in our research and development activities. We also expect to continue to incur increased expenses associated with operating as a public company, including increased costs of accounting, audit, legal, regulatory and tax-related services attributable to maintaining compliance with exchange listing standards and Securities and Exchange Commission, or SEC, requirements, director and officer insurance costs and investor and public relations costs.

We also expect to incur additional intellectual property-related expenses as we file patent applications to protect intellectual property arising from our research and development activities.

Other Income (Expense), Net

Other income (expense), net consists primarily of interest income earned from our cash and cash equivalents. This interest income is partially offset by interest expense principally on the note payable under our debt arrangement with PacWest and gains or losses associated with changes in the fair value of contingent liabilities associated with the consummation of specified transactions, including our IPO. Upon completion of our IPO in October 2021, our contingent liability with PacWest and our other contingent derivative liability became due and payable. These fees were paid during the fourth quarter of 2021 and as a result, no further gains or losses will be recognized related to those contingent liabilities.

Income Taxes

Since our inception, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in each year or for our earned research and development tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2022, we had federal and state net operating loss, or NOL, carryforwards of $177.5 million and $146.6 million, respectively, which may be available to offset future taxable income. As of December 31, 2022, federal NOLs of $172.7 million have an indefinite carryforward period. The remaining federal NOL carryforwards and our state NOL carryforward will expire beginning in 2035. These loss carryforwards are available to reduce future federal taxable income, if any. As of December 31, 2022, we also had federal and state research and development carryforwards of approximately $5.2 million and $2.5 million, respectively, which may be available to offset any future income tax and which will begin to expire in 2033. These loss and credit carryforwards are subject to review and possible adjustment by the appropriate taxing authorities.

Utilization of our NOL carryforwards and research and development credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future in accordance with Section 382 of the Internal Revenue Code of 1986, or Section 382, as well as similar state provisions. These ownership changes may limit the amount of NOL and research and development credit carryforwards that can be utilized annually to offset future taxable income and taxes, respectively. In general, an ownership change as defined by Section 382 results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. Since our formation, we have raised capital through the issuance of units and capital stock on several occasions. These financings may have resulted in a change of control as defined by Section 382. We have not yet completed a detailed study of our inception to date ownership change activity.

In addition, we have not yet conducted a study of our research and development credit carry forwards. Such a study may result in an adjustment to our research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amount is being presented as an uncertain tax position. A full valuation allowance has been provided against our research and development credits, and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the balance sheet or statement of operations and comprehensive loss if an adjustment were required.

Income taxes are determined at the applicable tax rates adjusted for non-deductible expenses, research and development tax credits and other permanent differences. Our income tax provision may be significantly affected by changes to our estimates.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Operating expenses			
Research and development	$ 59,201	$ 51,188	$ 8,013
General and administrative	29,948	23,856	6,092
Total operating expenses	89,149	75,044	14,105
Loss from operations	(89,149)	(75,044)	(14,105)
Other income (expense), net			
Other income (expense), net	927	(756)	1,683
Total other income (expense), net	927	(756)	1,683
Net loss	$ (88,222)	$ (75,800)	$ (12,422)

Research and Development Expenses

The following table summarizes our research and development expenses for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2022	2021	Change
XTX101	$ 6,374	$ 5,941	$ 433
XTX202	6,249	14,143	(7,894)
XTX301	11,475	4,697	6,778
Other early programs and indirect research and development	14,037	10,595	3,442
Personnel-related (including equity-based compensation)	21,066	15,812	5,254
Total research and development expenses	$ 59,201	$ 51,188	$ 8,013

Research and development expenses increased by $8.0 million from $51.2 million for the year ended December 31, 2021 to $59.2 million for the year ended December 31, 2022. The increase in research and development expenses was primarily due to the following:

- $6.8 million increase in expenses incurred in connection with XTX301, primarily driven by an increase of approximately $4.6 million in manufacturing activities, an increase of approximately $1.2 million related to preclinical development activities and an increase of approximately $1.0 million in clinical development activities related to our Phase 1 clinical trial for XTX301;

- $5.3 million increase in personnel-related costs, primarily driven by higher research and development headcount and a corresponding increase of approximately $4.2 million in salaries, bonuses and benefits, and an increase of approximately $1.1 million in equity-based compensation;

- $3.4 million increase in other early programs and indirect research and development expenses, primarily driven by an increase in manufacturing activities and external expenses related to preclinical research and development activities; and

- $2.8 million increase in clinical development activities related to our Phase 1 clinical trial for XTX202, which were offset by decreases in manufacturing expenses and preclinical expenses for XTX202 of approximately $6.6 million and $3.8 million, respectively, as the program advanced further into clinical development in 2022.

General and Administrative Expenses

The following table summarizes our general and administrative expenses for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Personnel-related (including equity-based compensation)	$ 16,701	$ 12,708	$ 3,993
Professional and consulting fees	7,556	8,248	(692)
Facility-related and other general and administrative expenses	5,691	2,900	2,791
Total general and administrative expenses	$ 29,948	$ 23,856	$ 6,092

General and administrative expenses increased by $6.1 million from $23.9 million for the year ended December 31, 2021 to $29.9 million for the year ended December 31, 2022. The increase in general and administrative expenses was primarily due to the following:

- $4.0 million increase in personnel-related costs, primarily driven by higher general and administrative headcount and a corresponding increase of approximately $2.3 million in salaries, bonuses and benefits, and an approximately $2.3 million increase in equity-based compensation, which includes approximately $0.6 million in non-recurring compensation expense resulting from the modification of previously issued stock options, partially offset by a decrease of approximately $0.6 million in recruiting costs;

- $2.8 million increase in facility-related and other general and administrative expenses, primarily driven by increases in costs incurred as a result of becoming a publicly traded company, including directors' and officers' liability insurance and other corporate related costs associated with increased overall corporate headcount; and

- These increases were partially offset by a $0.7 million decrease in professional and consulting fees.

Other Income (Expense), Net

Other income (expense), net changed by $1.7 million from other expense of $0.8 million for the year ended December 31, 2021 to other income of $0.9 million for the year ended December 31, 2022. The change in other income (expense), net was primarily due to an increase in interest income earned from higher interest rates on higher average cash balances as a result of the net proceeds received from our IPO.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception, we have incurred significant operating losses and negative cash flows from operations. We have not yet commercialized any of our product candidates, which are in preclinical or early clinical development, and we do not expect to generate revenue from sales of any products for several years, if at all. To date, we have financed our operations primarily from proceeds raised through private placements of preferred units and convertible preferred stock, a debt financing and our IPO. Through December 31, 2022, we have received an aggregate of $350.9 million in net proceeds from such transactions, including aggregate net proceeds of $116.4 million from our IPO, an aggregate of $224.5 million in net proceeds from the sale and issuance of preferred units and convertible preferred stock, and $10.0 million in net proceeds from our debt financing with PacWest. As of December 31, 2022, we had cash and cash equivalents of $120.4 million.

In November 2022, we entered into a sales agreement with Cowen, under which we may issue and sell shares of our common stock, from time to time, having an aggregate offering price of up to $75.0 million, subject to the terms and conditions of the sales agreement. As of December 31, 2022, we have not issued or sold any of our common stock pursuant to the sales agreement and $75.0 million of shares of common stock remain available to be sold pursuant to the sales agreement, which sales, if any, would be made under our 2022 Shelf.

Cash Flows

The following table provides information regarding our cash flows for each period presented (in thousands):

	Year Ended December 31,	
	2022	2021
Net cash provided by (used in):		
Operating activities	$ (75,723)	$ (80,751)
Investing activities	(1,867)	(1,100)
Financing activities	(69)	260,668
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (77,659)	$ 178,817

Operating Activities

Our cash flows from operating activities are greatly influenced by our use of cash for operating expenses and working capital requirements to support our business. We have historically experienced negative cash flows from operating activities as we invested in research and development of our product candidates, including preclinical studies, clinical trials, manufacturing and manufacturing process development. The cash used in operating activities resulted primarily from our net losses adjusted for non-cash charges, which are generally due to equity-based compensation, depreciation and amortization, as well as changes in components of operating assets and liabilities, which are generally due to increased expenses and timing of vendor payments.

During the year ended December 31, 2022, net cash used in operating activities of $75.7 million was primarily due to our net loss of $88.2 million, partially offset by net non-cash expenses of $10.5 million and changes in operating assets and liabilities of $2.0 million.

During the year ended December 31, 2021, net cash used in operating activities of $80.8 million was primarily due to our net loss of $75.8 million and changes in operating assets and liabilities of $11.8 million, partially offset by net non-cash expenses of $6.9 million.

Investing Activities

During the years ended December 31, 2022 and 2021, net cash used in investing activities of $1.9 million and $1.1 million, respectively, was primarily due to purchases of property and equipment.

Financing Activities

During the year ended December 31, 2022, net cash used in financing activities of $0.1 million consisted primarily of payments on our finance lease for certain lab equipment, partially offset by proceeds received from the exercise of stock options.

During the year ended December 31, 2021, net cash provided by financing activities of $260.7 million consisted primarily of proceeds from the sale and issuance of our Series B convertible preferred stock, the sale and issuance of our Series C convertible preferred stock and from the sale and issuance of common stock from our IPO.

Capital Requirements

We expect our future capital requirements to increase substantially over time in connection with our ongoing research and development activities, particularly as we advance our current and planned clinical development of our product candidates and expand the research efforts and preclinical activities associated with our other existing programs and discovery platform. In addition, we expect to continue to incur additional costs associated with operating as a public company. As a result, we expect to incur substantial operating losses and negative operating cash flows for the foreseeable future.

Inflation generally affects us by increasing our cost of labor and certain services. We do not believe that inflation had a material effect on our financial statements included elsewhere in this Annual Report on Form 10-K. However, the United States has recently experienced historically high levels of inflation. If the inflation rate continues to increase it may affect our expenses, such as employee compensation and research and development charges due to, for example, increases in the costs of labor and supplies. Additionally, the United States is experiencing a workforce shortage, which in turn has created a competitive wage environment that may also increase our operating costs in the future.

As of December 31, 2022, we had cash and cash equivalents of $120.4 million. We believe that our existing cash and cash equivalents will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2024. 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.

Because of the numerous risks and uncertainties associated with product development, and because the extent to which we may enter into collaborations with third parties for the development of our product candidates is unknown, we may incorrectly estimate the timing and amounts of increased capital outlays and operating expenses associated with advancing the research and development of our product candidates. Our funding requirements and timing and amount of our operating expenditures will depend on many factors, including, but not limited to:

- the scope, progress, results and costs of research and development for our current and future product candidates, including our current and planned clinical trials for our clinical-stage cytokine product candidates, XTX202 and XTX301, and ongoing preclinical development for our current and future product candidates;

- the scope, prioritization and number of our research and development programs;

- the scope, costs, timing and outcome of regulatory review of our product candidates;

- the costs of securing manufacturing materials for use in preclinical studies, clinical trials and, for any product candidates for which we receive regulatory approval, if any, commercial supply;

- the costs and timing of future commercialization activities for any of our product candidates for which we receive regulatory approval;

- the amount and timing of revenue, if any, received from commercial sales of any product candidates for which we receive regulatory approval;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims;

- the extent to which we may acquire or in-license other products, product candidates, technologies or intellectual property, as well as the terms of any such arrangements;

- our ability to seek, establish and maintain a collaboration to further develop XTX101, our Fc-enhanced, tumor-activated anti-CTLA-4, with a collaborator, including the financial terms and any cost-sharing arrangements of any such collaboration; and

- the costs of continuing to expand our operations and operating as a public company.

Identifying potential product candidates and conducting preclinical studies and clinical trials is a time consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if ever. Accordingly, we will need to obtain substantial additional capital to achieve our business objectives.

Our expectation with respect to our ability to fund our currently planned operations is based on estimates that are subject to various risks and uncertainties. Our operating plan may change as a result of many factors currently unknown to management and there can be no assurance that our current operating plan will be achieved in the time frame anticipated by us, and we may need to seek additional capital sooner than anticipated.

Adequate additional capital may not be available to us on acceptable terms, or at all. Market volatility resulting from the COVID-19 pandemic, adverse changes in domestic and international fiscal, monetary and other policies and political relations, regional or global conflicts, uncertainty around global economic conditions, or other factors could also adversely impact our ability to access capital as and when needed. To the extent that we raise additional capital through the sale of equity or securities convertible into or exchangeable for equity, the ownership interest of our existing stockholders may be diluted, and the terms of such securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. Additional debt and preferred equity, if available, may also involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require that we issue warrants, which could potentially dilute the ownership interest of our existing stockholders.

If we raise additional capital through collaborations, partnerships, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our intellectual property, future revenue streams, research programs or product candidates or products, and we may be required to grant licenses on terms that may not be favorable to us. If we are unable to raise additional capital through equity or debt offerings when needed, we may have to significantly delay, reduce or eliminate some or all of our product development or future commercialization efforts, or grant rights to develop and market product candidates or products that we would have otherwise preferred to develop and market ourselves.

Contractual Obligations

In the normal course of business, we enter into agreements that contain contractual obligations, of which the most significant to date include our loan and security agreement with PacWest, an operating lease for our corporate headquarters and certain license agreements.

Loan and Security Agreement

In November 2019, we entered into a loan and security agreement with PacWest, as amended, which we refer to as the loan agreement, under which we borrowed $10.0 million under a term loan, which amount remains outstanding. Borrowings under the loan agreement are collateralized by substantially all of our assets, excluding intellectual property. Interest on amounts outstanding accrues at a variable annual rate equal to the greater of (i) the prime rate plus 0.25% or (ii) 4.75%. As of December 31, 2022, the interest rate on the term loan is 7.75%. We were required to make interest-only payments on any outstanding balances through December 31, 2022. We commenced making equal monthly payments of principal plus interest in January 2023, and we will be required to make such payments until the term loan matures on June 30, 2024. Under the loan agreement, we paid a one-time success fee of $0.8 million to PacWest in the fourth quarter of 2021 upon the closing of our IPO.

The loan agreement contains customary representations, warranties and covenants and also includes customary events of default, including payment defaults, breaches of covenants, a change of control and occurrence of a material adverse effect.

Lease Agreement

We lease building space for our corporate headquarters at 828 Winter Street in Waltham, Massachusetts under a non-cancellable operating lease that expires in March 2030. Our operating lease includes the option to extend the term for a period of five years at the then-market rental rate. As of December 31, 2022, the remaining required payments for our operating lease, not including the optional extension period, are approximately $13.4 million. For further information regarding our operating lease agreement, please see Note 8, *Leases,* to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Other Contractual Obligations

We are party to certain agreements that require us to pay third parties upon achievement of certain development, regulatory or commercial milestones or upon the consummation of specified transactions. Amounts related to contingent payments are not considered contractual obligations as they are contingent on the successful achievement of certain development, regulatory and commercial milestones that may not be achieved or upon the consummation of specified transactions that may not occur. We have not included payments contingent upon the achievement of certain development, regulatory or commercial milestones on our consolidated balance sheets. For further information regarding certain of our license agreements and amounts that could become payable in the future under those agreements, please see Note 7, *Intellectual Property Licenses,* to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

In addition, we are party to certain agreements with contract research organizations for clinical trials and clinical supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. Such contracts are generally cancellable by us for convenience with up to 90 days of notice. We may be subject to certain termination fees or wind-down costs upon termination of these agreements. The exact amount of such costs are generally not fixed or estimable.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of these consolidated 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 the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on 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 our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies used in the preparation of our consolidated financial statements require the most significant judgments and estimates.

Research and Development Expenses and Related Accruals

Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries, equity-based compensation and benefits, facilities costs and laboratory supplies, depreciation, manufacturing expenses and external costs of outside vendors engaged to conduct planned clinical development, preclinical development, manufacturing and manufacturing process development and other research support activities. All costs associated with research and development activities are expensed as incurred.

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual

cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with certain service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our vendors in connection with research and development activities for which we have not yet been invoiced. In certain instances, we prepay for services to be provided in the future. These amounts are initially capitalized and subsequently expensed as the services are performed.

We base our expenses related to research and development activities on our estimates of the services received and efforts expended pursuant to quotes and contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid balance accordingly. Nonrefundable advance payments for goods and services that will be used in future research and development activities are initially capitalized and subsequently expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting accrued amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts incurred.

Equity-Based Compensation

We issue equity-based awards to employees, directors and non-employees, generally in the form of stock options. We measure employee equity-based compensation based on the grant date fair value of the equity-based awards and recognize equity-based compensation expense on a straight-line basis over the requisite service period of the awards, which is generally the vesting period of the respective award, in accordance with Financial Accounting Standards Board Accounting Standards Codification Topic 718, *Compensation—Stock Compensation*, or ASC 718. For awards subject to performance conditions, we recognize equity-based compensation expense using an accelerated recognition method over the remaining period when we determine that achievement of the milestone is probable. We recognize forfeitures as they occur. We classify equity-based compensation expense in the consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified, as applicable.

Determination of the Fair Value of Equity-Based Awards

We estimate the fair value of our stock options granted with service-based conditions using the Black-Scholes option pricing model, which requires inputs of subjective assumptions, including: (i) the expected volatility of our common stock, (ii) the expected term of the award, (iii) the risk-free interest rate, (iv) expected dividends and (v) the fair value of our common stock. We completed our IPO in October 2021, and as a result there has not been a significant amount of time for which there has been a public market for the trading of our common stock, including a lack of company-specific historical and implied volatility data, therefore we base the estimate of expected volatility on the historical volatilities of a representative group of publicly traded guideline companies. For these analyses, we select companies with comparable characteristics and with historical share price information that approximates the expected term of the equity-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period that approximates the calculated expected term of our stock options. We will continue to apply this method until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected term of our stock options granted to employees and directors using the simplified method, whereby the expected term equals the average of the vesting term and the original contractual term of the option. We utilize this method as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term and the plain nature of our equity-based awards. The expected dividend yield is assumed to be

zero as we have no current plans to pay any dividends on common stock. We have elected to use the expected term for stock options granted to non-employees, using the simplified method, as the basis for the expected term assumption. However, we may elect to use either the contractual term or the expected term for stock options granted to non-employees on an award-by-award basis.

Determination of Fair Value of Common Stock

Subsequent to the completion of our IPO in October 2021, the fair value of our common stock has been determined based on the share price of our common stock on the Nasdaq Global Select Market. If applicable, the current share price is adjusted to reflect material nonpublic information known to the company but unavailable to market participants at the time of the grant.

Prior to the completion of our IPO in October 2021, there was no public market for our common stock. The estimated fair value of our common stock was approved by our board of directors, with input from management, as of the date of each award grant, considering the most recently available independent third-party valuations of our common stock and our board of directors assessment, with input from management, of additional objective and subjective factors that we believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. These independent third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. We estimated the value of our equity using market approaches. The market approach includes using the market adjusted equity value method, guideline initial public offering, or IPO, transactions method and the recent transaction method which "back solves" to a preferred price. The hybrid approach is a scenario-based analysis and where one or more of the scenarios allocate the equity value utilizing the option-pricing method, or OPM. We allocated equity value to our shares of common stock and shares of our convertible preferred stock, as the case may be, using either an OPM or a hybrid method, which is a hybrid between the OPM and the probability-weighted expected return method. The OPM treats common securities and preferred securities as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the common stock has value only if the funds available for distribution to members exceed the value of the preferred security liquidation preference at the time of the liquidity event, such as a strategic sale or a merger. When using the market approach to determine the equity value, we allocated the equity value to our shares of common stock, warrants and shares of our convertible preferred stock, as the case may be, using the OPM. When using the hybrid approach, we estimated the probability-weighted value across multiple scenarios but used the OPM to estimate the allocation of value within at least one of the scenarios. In addition to a scenario using the OPM, the hybrid method also considers an IPO scenario in which the shares of convertible preferred stock are assumed to convert to common stock. The future value of the common stock in the IPO scenario was discounted back to the valuation date at an appropriate risk adjusted discount rate. In the hybrid method, the present value indicated for each scenario was probability weighted to arrive at an indication of value for our common stock.

In addition to considering the results of these third-party valuations, our board of directors considered various objective and subjective factors to determine the fair value of our equity instruments as of each grant date, which may have been later than the most recently available third-party valuation date, including:

- the lack of liquidity of our equity as a private company;
- the prices of our convertible preferred stock sold to outside investors in arm's length transactions and the rights, preferences and privileges of our convertible preferred stock as compared to those of our common stock, including the liquidation preferences of our convertible preferred stock;
- the progress of our research and development efforts, including the status of preclinical studies for our product candidates;
- our stage of development and business strategy and the material risks related to our business and industry;
- the achievement of enterprise milestones, including entering into strategic collaborative and license agreements;

- the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies;

- any external market conditions affecting the biotechnology industry and trends within the biotechnology industry;

- the likelihood of achieving a liquidity event, such as an initial public offering or a sale of our company, given prevailing market conditions; and

- the analysis of initial public offerings and the market performance of similar companies in the biotechnology industry.

There are significant judgments and estimates inherent in these valuations. These judgments and estimates included assumptions regarding our future operating performance, the stage of development of our product candidates, the timing and probability of a potential initial public offering or other liquidity event and the determination of the appropriate valuation methodology at each valuation date. The assumptions underlying these valuations represented management's best estimates, which involved inherent uncertainties and the application of management judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our equity-based compensation expense could be materially different.

Emerging Growth Company and Smaller Reporting Company Status

As an emerging growth company, or EGC, under the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we may delay the adoption of certain accounting standards until such time as those standards apply to private companies. Other exemptions and reduced reporting requirements under the JOBS Act for EGCs include presentation of only two years of audited financial statements in a registration statement for an IPO, an exemption from the requirement to provide an auditor's report on internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, an exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation, and less extensive disclosure about our executive compensation arrangements.

In addition, the JOBS Act provides that an EGC can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an EGC to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we can adopt the new or revised standard at the time private companies adopt the new or revised standard and may do so until such time that we either (1) irrevocably elect to "opt out" of such extended transition period or (2) no longer qualify as an emerging growth company. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We may remain classified as an EGC until December 31, 2026, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.235 billion or more in any fiscal year, we would cease to be an emerging growth company as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1 billion of non-convertible debt over a three-year period.

We are also a "smaller reporting company," meaning that the market value of our shares held by non-affiliates is less than $700 million and our annual revenue was less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our shares held by non-affiliates is less than $250 million or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our shares held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies.

Recent Accounting Pronouncements

For a description of recent accounting pronouncements, see Note 2 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are a smaller reporting company, as defined by Rule 12b-2 of the Securities Exchange Act of 1934, as amended, and are not required to provide the information required under this item.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15, Exhibits and Financial Statement Schedules, 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

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Our Chief Executive Officer (our principal executive and financial officer) evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. Based upon such evaluation, our Chief Executive Officer has concluded that, as of December 31, 2022, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

Internal control over financial reporting refers to the process designed by, or under the supervision of, our principal executive and financial officer, and effected by our Board of Directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of consolidated financial statements for external purposes in accordance with generally accepted accounting principles, and includes those policies and procedures that:

(1) pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;

(2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of consolidated financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

(3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the consolidated financial statements.

Internal control over financial reporting cannot provide absolute assurance of achieving financial reporting objectives because of its inherent limitations. Internal control over financial reporting is a process that involves human diligence and compliance and is subject to lapses in judgment and breakdowns resulting from human failures. Internal control over financial reporting also can be circumvented by collusion or improper management override. Also, projections of any evaluation of effectiveness of internal control over financial reporting to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with policies or procedures may deteriorate. Because of such limitations, there is a risk that material misstatements may not be prevented or detected on a timely basis by internal control over financial reporting. However, these inherent limitations are known features of the financial reporting process. Therefore, it is possible to design into the process safeguards to reduce, though not eliminate, this risk.

Management is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Under the supervision and with the participation of our management, including our principal executive and financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting. Management has used the framework set forth in the report entitled "Internal Control—Integrated Framework (2013)" published by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) to evaluate the effectiveness of our internal control over financial reporting. Based on its evaluation, management has concluded that our internal control over financial reporting was effective as of December 31, 2022.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for "emerging growth companies".

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that occurred during the period covered by this Annual Report on Form 10-K that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

On March 1, 2023, Michael Ross, Ph.D., notified us of his resignation as a Class III member of our board of directors, effective immediately. Dr. Ross' resignation did not result from any disagreement with us on any matter relating to our operations, policies or practices. Upon the recommendation of the nominating and corporate governance committee, our board of directors unanimously appointed Christy Rossi, a current member of the board of directors, to serve on the audit committee.

Item 9C. Disclosure Regarding Foreign Jurisdictions That Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Except to the extent provided below, the information required by this Item 10 will be included in our definitive proxy statement to be filed with the Securities and Exchange Commission, or the SEC, with respect to our 2023 Annual Meeting of Stockholders within 120 days of the end of the fiscal year to which this report relates, which information is incorporated herein by reference.

We post our Code of Business Conduct and Ethics, which applies to our directors, officers, and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions, in the "Corporate Governance" sub-section of the "Investor Relations" section (ir.xiliotx.com) of our corporate website https://xiliotx.com/. We intend to disclose on our website any amendments to, or waivers from, the Code of Business Conduct and Ethics that are required to be disclosed pursuant to the disclosure requirements of Item 5.05 of Form 8-K. Our website is not incorporated by reference into this Annual Report on Form 10-K and you should not consider any information contained in or accessible from our website to be a part of this Annual Report on Form 10-K.

Item 11. Executive Compensation

The information required by this Item 11 will be included in the section captioned "Executive Compensation" in our definitive proxy statement for our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates, which information is incorporated herein by reference.

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

The information required by this Item 12 will be included in the section captioned "Security Ownership of Certain Beneficial Owners and Management" in our definitive proxy statement for our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates, which information is incorporated herein by reference.

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

The information required by this Item 13 will be included in the sections captioned "Related Person Transactions," "Policies for Related Person Transactions" and "Director Independence" in our definitive proxy statement for our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates, which information is incorporated herein by reference.

Item 14. Principal Accountant's Fees and Services

The information required by this Item 14 will be included in the section captioned "Audit Fees and Services" our definitive proxy statement for our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates, which information is incorporated herein by reference.

Part IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

The following documents are included on pages set forth in Part II, Item 8 of this Annual Report on Form 10-K and are filed as part of this Annual Report on Form 10-K.

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(2) Financial Statement Schedules

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(3) Exhibits

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

EXHIBIT INDEX

		Incorporated by Reference			
Exhibit Number	**Description of Exhibit**	**Form**	**File No.**	**Exhibit Number**	**Filing Date**
1.1	Sales Agreement, dated September 9, 2022, by and between the Registrant and Cowen and Company, LLC	S-3	333-268264	1.2	November 9, 2022
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-40925	3.1	October 26, 2021
3.2	Amended and Restated Bylaws of the Registrant	8-K	001-40925	3.2	October 26, 2021
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1	333-259973	4.1	October 1, 2021
4.2	Amended and Restated Registration Rights Agreement, dated as of February 23, 2021, by and among the Registrant and the other parties thereto	S-1	333-259973	10.1	October 18, 2021
4.3	Description of the Registrant's securities registered pursuant to Section 12 of the Securities and Exchange Act of 1934, as amended	10-K	001-40925	4.3	March 1, 2022
10.1	2020 Stock Incentive Plan, as amended	S-1	333-259973	10.2	October 1, 2021
10.2	Form of Stock Option Agreement under 2020 Stock Incentive Plan	S-1	333-259973	10.3	October 1, 2021
10.3	Form of Restricted Stock Agreement under 2020 Stock Incentive Plan	S-1	333-259973	10.4	October 1, 2021
10.4	2021 Stock Incentive Plan	S-1	333-259973	10.5	October 18, 2021
10.5	Form of Stock Option Agreement under the 2021 Stock Incentive Plan	S-1	333-259973	10.6	October 18, 2021
10.6	Form of Non-Employee Director Stock Option Agreement under the 2021 Stock Incentive Plan	S-1	333-259973	10.7	October 18, 2021
10.7	2021 Employee Stock Purchase Plan	S-1	333-259973	10.8	October 18, 2021
10.8	2022 Inducement Stock Incentive Plan				*
10.9	Form of Stock Option Agreement under the 2022 Inducement Stock Incentive Plan				*
10.10	Form of Restricted Stock Unit Agreement under the 2022 Inducement Stock Incentive Plan				*
10.11	Loan and Security Agreement, dated as of November 21, 2019, as amended, by and between the Registrant and Pacific Western Bank	10-Q	001-40925	10.1	May 12, 2022
10.12#	Letter Agreement, dated September 30, 2021, by and between the Registrant and René Russo	S-1	333-259973	10.15	October 1, 2021
10.13#	Amended and Restated Employment Agreement, dated June 15, 2022, by and between the Registrant and Martin Huber, M.D.	8-K	001-40925	10.1	June 16, 2023

10.14	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-259973	10.20	October 1, 2021
10.15	Director Compensation Policy	S-1	333-259973	10.9	October 1, 2021
10.16†	Cross-License Agreement, dated as of December 16, 2020, by and between the Registrant and AskGene Pharma, Inc.	S-1	333-259973	10.11	October 1, 2021
10.17†	Amended and Restated Exclusive License Agreement, dated as of August 16, 2016, by and between the Registrant and City of Hope	S-1	333-259973	10.12	October 1, 2021
10.18†	License Agreement, dated as of September 26, 2016, as amended, by and between the Registrant and WuXi Biologics (Hong Kong) Limited	S-1	333-259973	10.13	October 1, 2021
10.19	Lease, dated as of August 26, 2019, as amended, by and between the Registrant and PPF off 828-830 Winter Street, LLC	S-1	333-259973	10.14	October 1, 2021
10.20#	Letter Agreement, dated September 30, 2021, by and between the Registrant and Salvatore Giovine	10-K	001-40925	10.20	March 1, 2022
21.1	Subsidiaries of the Registrant				*
23.1	Consent of Ernst & Young LLP, independent registered public accounting firm				*
31.1	Certification of Principal Executive and Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				*
32.1	Certification of Principal Executive and Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				*
101.INS	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				*
101.SCH	Inline XBRL Taxonomy Extension Calculation Linkbase Document				*
101.CAL	Inline XBRL Taxonomy Extension Definition Linkbase Document				*
101.DEF	Inline XBRL Taxonomy Extension Label Linkbase Document				*
101.LAB	Inline XBRL Taxonomy Extension Presentation Linkbase Document				*
104	Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101)				

* Filed herewith.

\# Indicates management contract or compensatory plan or arrangement.

† Portions of this exhibit have been omitted pursuant to Item 601 of Regulation S-K promulgated under the Securities Act because the information is not material and is a type of information that the registrant treats as private or confidential.

Item 16. Form 10-K Summary

None.

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.

XILIO THERAPEUTICS, INC.

Date: March 2, 2023

By: /s/ René Russo
René Russo
Chief Executive Officer

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

Signature	Title	Date
/s/ René Russo René Russo	Chief Executive Officer and Director *(Principal Executive and Financial Officer)*	March 2, 2023
/s/ Brian King Brian King	Controller *(Controller)*	March 2, 2023
/s/ Paul J. Clancy Paul J. Clancy	Chairman of the Board	March 2, 2023
/s/ Sara M. Bonstein Sara M. Bonstein	Director	March 2, 2023
/s/ Daniel Curran Daniel Curran	Director	March 2, 2023
/s/ Tomas J. Heyman Tomas J. Heyman	Director	March 2, 2023
/s/ Robert Ross Robert Ross	Director	March 2, 2023
/s/ Christina Rossi Christina Rossi	Director	March 2, 2023
/s/ Yuan Xu Yuan Xu	Director	March 2, 2023

Xilio Therapeutics, Inc.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Xilio Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Xilio Therapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the years then ended in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. 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/ Ernst & Young LLP

We have served as the Company's auditor since 2020.

Boston, Massachusetts

March 2, 2023

XILIO THERAPEUTICS, INC.

CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31, 2022	December 31, 2021
ASSETS		
Current assets		
Cash and cash equivalents	$ 120,385	$ 198,053
Prepaid expenses and other current assets	4,111	4,464
Total current assets	124,496	202,517
Restricted cash	1,562	1,553
Property and equipment, net	7,255	7,620
Operating lease right-of-use asset	5,585	5,977
Other non-current assets	267	393
Total assets	$ 139,165	$ 218,060
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities		
Accounts payable	$ 3,125	$ 3,144
Accrued expenses	10,327	8,751
Operating lease liability, current portion	918	801
Notes payable, current portion	6,667	—
Other current liabilities	82	82
Total current liabilities	21,119	12,778
Notes payable, net of current portion	3,165	9,628
Operating lease liability, net of current portion	9,189	10,107
Other liabilities, long-term	45	118
Total liabilities	33,518	32,631
Commitments and contingencies (Note 9)		
Stockholders' equity		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized at December 31, 2022 and December 31, 2021, no shares issued or outstanding at December 31, 2022 and December 31, 2021	—	—
Common stock, $0.0001 par value; 200,000,000 shares authorized at December 31, 2022 and December 31, 2021; 27,471,607 shares issued and 27,425,447 shares outstanding at December 31, 2022; 27,468,950 shares issued and 27,358,375 shares outstanding at December 31, 2021	3	3
Additional paid-in capital	354,752	346,312
Accumulated deficit	(249,108)	(160,886)
Total stockholders' equity	105,647	185,429
Total liabilities and stockholders' equity	$ 139,165	$ 218,060

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

XILIO THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share data)

	Year Ended December 31,	
	2022	2021
Operating expenses		
Research and development	$ 59,201	$ 51,188
General and administrative	29,948	23,856
Total operating expenses	89,149	75,044
Loss from operations	(89,149)	(75,044)
Other income (expense), net		
Other income (expense), net	927	(756)
Total other income (expense), net	927	(756)
Net loss and comprehensive loss	$ (88,222)	$ (75,800)
Net loss per share, basic and diluted	$ (3.22)	$ (13.52)
Weighted average common shares outstanding, basic and diluted	27,392,087	5,606,308

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

XILIO THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share data)

	Series A Convertible Preferred Stock		Series A-1 Convertible Preferred Stock		Series B Convertible Preferred Stock		Series C Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2020	7,500,000	$ 7,309	19,565,216	$ 20,740	39,723,312	$ 49,953	—	$ —	689,929	$ —	$ 1,799	$ (85,086)	$ (83,287)
Issuance of Series B convertible preferred stock, net of issuance costs of $50	—	—	—	—	39,723,312	50,200	—	—	—	—	—	—	—
Issuance of Series C convertible preferred stock, net of issuance costs of $314	—	—	—	—	—	—	68,271,641	94,686	—	—	—	—	—
Conversion of convertible preferred stock into common stock upon initial public offering	(7,500,000)	(7,309)	(19,565,216)	(20,740)	(79,446,624)	(100,153)	(68,271,641)	(94,686)	18,398,248	2	222,886	—	222,888
Issuance of common stock upon initial public offering, net of issuance costs of $13,547	—	—	—	—	—	—	—	—	8,119,106	1	116,358	—	116,359
Conversion of warrant liability to equity upon initial public offering	—	—	—	—	—	—	—	—	—	—	28	—	28
Vesting of restricted common stock	—	—	—	—	—	—	—	—	103,192	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	—	—	47,900	—	283	—	283
Equity-based compensation expense	—	—	—	—	—	—	—	—	—	—	4,958	—	4,958
Net loss	—	—	—	—	—	—	—	—	—	—	—	(75,800)	(75,800)
Balance at December 31, 2021	—	$ —	—	$ —	—	$ —	—	$ —	27,358,375	$ 3	$ 346,312	$ (160,886)	$ 185,429
Vesting of restricted common stock	—	—	—	—	—	—	—	—	64,415	—	—	—	—
Exercise of stock options	—	—	—	—	—	—	—	—	2,657	—	16	—	16
Equity-based compensation expense	—	—	—	—	—	—	—	—	—	—	8,424	—	8,424
Net loss	—	—	—	—	—	—	—	—	—	—	—	(88,222)	(88,222)
Balance at December 31, 2022	—	$ —	—	$ —	—	$ —	—	$ —	27,425,447	$ 3	$ 354,752	$ (249,108)	$ 105,647

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

XILIO THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (88,222)	$ (75,800)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	1,847	1,499
Non-cash interest expense	223	173
Equity-based compensation expense	8,424	4,958
Loss on disposal of property and equipment	1	19
Change in fair value of warrant and derivative liabilities	—	203
Changes in operating assets and liabilities:		
Prepaid and other assets	344	(3,136)
Operating lease right-of-use asset	391	332
Accounts payable	485	(2,818)
Accrued expenses and other liabilities	1,585	(5,617)
Operating lease liability	(801)	(564)
Net cash used in operating activities	(75,723)	(80,751)
Cash flows from investing activities:		
Purchases of property and equipment	(1,867)	(1,100)
Net cash used in investing activities	(1,867)	(1,100)
Cash flows from financing activities:		
Repayments of debt principal	—	(1,000)
Proceeds from debt issuance, net of issuance costs	—	975
Payments of finance lease	(85)	(85)
Payment of success fee	—	(750)
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	144,886
Proceeds from initial public offering, net of issuance costs	—	116,359
Proceeds from exercise of stock options	16	283
Net cash (used in) provided by financing activities	(69)	260,668
(Decrease) increase in cash, cash equivalents and restricted cash	(77,659)	178,817
Cash, cash equivalents and restricted cash, beginning of period	199,606	20,789
Cash, cash equivalents and restricted cash, end of period	$ 121,947	$ 199,606
Supplemental cash flow disclosure:		
Cash paid for interest	$ 555	$ 492
Supplemental disclosure of non-cash activities:		
Conversion of convertible preferred stock into common stock upon initial public offering	$ —	$ 222,888
Capital expenditures included in accounts payable or accrued expenses	$ 19	$ 539
Recognition of derivative liability in connection with long-term debt facility	$ —	$ 250
Conversion of warrant liability to equity upon initial public offering	$ —	$ 28

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

XILIO THERAPEUTICS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Description of Business, Initial Public Offering and Liquidity and Capital Resources

Description of Business

Xilio Therapeutics, Inc. ("Xilio" or the "Company") is a clinical-stage biotechnology company focused on harnessing the immune system to achieve deep and durable clinical responses to improve the lives of patients with cancer. The Company was incorporated in Delaware in June 2020, and its headquarters are located in Waltham, Massachusetts.

Initial Public Offering

In the fourth quarter of 2021, the Company completed its initial public offering ("IPO") of common stock, in which it issued and sold an aggregate of 8,119,106 shares of its common stock, including 766,106 shares pursuant to the partial exercise by the underwriters of their option to purchase additional shares, at a public offering price of $16.00 per share. The Company received $116.4 million in net proceeds, after deducting underwriting discounts and commissions and offering expenses payable by the Company.

Liquidity and Capital Resources

Since its inception, the Company has devoted substantially all of its financial resources and efforts to research and development activities. The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including but not limited to, risks associated with the successful research, development and manufacturing of product candidates, and, if approved, any products, obtaining regulatory approvals for product candidates, and, if approved, commercialization of any products, protection and enforcement of intellectual property and proprietary technology, development by third parties of potentially competitive products or product candidates, compliance with governmental regulations, and the ability to secure additional capital to fund operations. Programs currently under development will require significant additional research and development efforts, including preclinical and clinical testing and manufacturing process development and will need to obtain regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

As of December 31, 2022, the Company had cash and cash equivalents of $120.4 million. The Company believes that its existing cash and cash equivalents will be sufficient to enable the Company to fund its operating expenses and capital expenditure requirements into the second quarter of 2024, which is at least twelve months from the date of issuance of these consolidated financial statements. The Company expects to continue to generate negative cash flows from operations and net losses for the foreseeable future and will need additional capital in the future to support its continuing operations and growth strategy as it continues to invest significantly in research and development of its product candidates, including preclinical and clinical testing and manufacturing process development. To date, the Company has primarily funded its operations with proceeds from the sale of preferred units and convertible preferred stock, a debt financing and the IPO. Management's conclusion with respect to its ability to fund operations is based on estimates that are subject to risks and uncertainties that may prove to be incorrect. If actual results differ from management's estimates, the Company may be required to seek additional capital sooner or curtail planned activities to reduce operating expenses, which may have an adverse impact on the Company's ability to achieve its business objectives.

2. Summary of Significant Accounting Policies

Basis of Presentation

These consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States ("GAAP") and pursuant to the rules and regulations of the United States Securities and Exchange Commission (the "SEC"). Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP

as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

In April 2012, the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act") was enacted. Section 107(b) of the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. The Company has elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, the Company can adopt the new or revised standard at the time private companies adopt the new or revised standard and may do so until such time that the Company either (1) irrevocably elects to "opt out" of such extended transition period or (2) no longer qualifies as an emerging growth company. The Company may take advantage of these exemptions up until December 31, 2026, or such earlier time that it is no longer an emerging growth company.

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries: Xilio Development, Inc. ("Xilio Development"), a Delaware corporation, and Xilio Securities Corporation, a Massachusetts corporation, created to buy, sell and hold securities. Effective as of September 30, 2022, the Company's wholly owned subsidiaries, Xilio Therapeutics, LLC and Xilio Concerto, LLC, were merged with and into Xilio Development, Inc., with Xilio Development, Inc. continuing as the surviving corporation. All intercompany accounts and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in accordance with GAAP requires management to make estimates and judgments that may affect the reported amounts of assets and liabilities and related disclosures of contingent assets and liabilities at the date of the financial statements and the related reporting of expenses during the reporting period. Management considers many factors in selecting appropriate financial accounting policies and controls and in developing the estimates and assumptions that are used in the preparation of these consolidated financial statements. Factors that may affect estimates include expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. Significant estimates of accounting reflected in these consolidated financial statements include, but are not limited to, estimates related to accrued expenses, contingent amounts payable to third parties upon the consummation of specified transactions, including an initial public offering, the valuation of equity-based compensation, including stock options and restricted common stock, useful life of long-lived assets and income taxes. Actual results could differ from those estimates.

Segment Information

The Company has one operating segment. Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision-maker in deciding how to allocate resources and assess performance. The Company's chief operating decision-maker is its chief executive officer. The Company and its chief operating decision-maker view the Company's operations and manage its business as a single operating segment. All of the Company's long-lived assets are held in the United States.

Cash Equivalents and Restricted Cash

The Company considers all short-term, highly liquid investments with original maturities of 90 days or less at acquisition date to be cash equivalents. Cash equivalents, which consist of money market accounts, are stated at fair value. Restricted cash primarily represents a letter of credit issued to the landlord of the Company's facility lease and is reflected in non-

current assets on the accompanying consolidated balance sheets. Cash, cash equivalents and restricted cash consists of the following (in thousands):

	December 31, 2022	December 31, 2021
Cash and cash equivalents	$ 120,385	$ 198,053
Restricted cash	1,562	1,553
Total cash, cash equivalents and restricted cash as shown on the consolidated statements of cash flows	$ 121,947	$ 199,606

Concentrations of Credit Risk and Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company holds all cash and cash equivalents at accredited financial institutions. Bank accounts in the United States are insured by the Federal Deposit Insurance Corporation ("FDIC") up to $250,000. As of December 31, 2022 and 2021, certain of the Company's primary operating accounts significantly exceeded the FDIC limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on a third-party manufacturer to supply material and manufacturing process development services for its product candidates and related research and development activities. These research and development programs and activities could be adversely affected by a significant interruption in the supply of such products and services which could have a material adverse effect on the Company's business, financial position and results of operations.

Fair Value Measurements

Certain assets and liabilities are carried at fair value under GAAP. 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. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- *Level 1*—Quoted prices in active markets for identical assets or liabilities.

- *Level 2*—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.

- *Level 3*—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

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

The carrying values of the Company's cash, prepaid expenses, accounts payable and accrued expenses approximate their fair value due to their short-term nature. The carrying value of the Company's outstanding debt as of December 31, 2022 and 2021 approximates fair value based on the variable interest rate for the borrowings as well as the short duration of the term of the note. Items measured at fair value on a recurring basis include cash equivalents, the preferred warrant and contingent liabilities associated with the consummation of specified transactions, including an initial public offering.

Property and Equipment

Property and equipment is stated at cost, net of accumulated depreciation and amortization. Depreciation and amortization are calculated using the straight-line method over the estimated useful lives of the assets, which are as follows:

	Estimated Useful Life
Computers and software	3 years
Laboratory equipment	5 years
Furniture and fixtures	5 years
Leasehold improvements	Shorter of the useful life or the remaining term of the lease

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in loss from operations. Expenditures for repairs and maintenance that do not improve or extend the lives of the respective assets are charged to expense as incurred, while costs of major additions and betterments are capitalized.

Impairment of Long-Lived Assets

The Company periodically evaluates its long-lived assets, which consist of property and equipment, and any leased assets, for impairment whenever events or changes in circumstances indicate that a potential impairment may have occurred. If such events or changes in circumstances arise, the Company compares the carrying amount of the long-lived assets to the estimated future undiscounted cash flows expected to be generated by the long-lived assets. If the estimated aggregate undiscounted cash flows are less than the carrying amount of the long-lived assets, an impairment charge, calculated as the amount by which the carrying amount of the assets exceeds the estimated fair value of the assets, is recorded. The estimated fair value of the long-lived assets is determined based on the estimated discounted cash flows expected to be generated from the long-lived assets. The Company did not recognize impairment charges during the years ended December 31, 2022 and 2021, respectively.

Leases

The Company determines if an arrangement is or contains a lease at inception. Operating leases are included in right-of-use lease assets ("ROU assets") and in both the current portion of lease liabilities and long-term lease liabilities on the Company's consolidated balance sheets. Lease expense for operating leases is recognized on a straight-line basis over the lease term as an operating expense in the consolidated statements of operations and comprehensive loss. Assets subject to finance leases are included in other non-current assets and the related lease obligation is included in other current liabilities and other long-term liabilities on the Company's consolidated balance sheets. Lease expense for finance leases is recognized as depreciation expense and interest expense in the consolidated statements of operations and comprehensive loss using the effective interest method. The Company has elected the short-term lease recognition exemption for short-term leases, which allows the Company not to recognize lease liabilities and ROU assets on the consolidated balance sheets for leases with an original term of twelve months or less.

ROU assets represent the Company's right to use an underlying asset for the lease term, and lease liabilities represent the Company's obligation to make lease payments arising from the lease. Operating lease liabilities and their corresponding ROU assets are initially recorded based on the present value of lease payments over the expected remaining lease term. When determining the lease term, the Company includes options to extend or terminate the lease when it is reasonably certain that the option will be exercised. Certain adjustments to the ROU asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments. The incremental borrowing rate reflects the fixed rate at which the Company could borrow, on a collateralized basis, the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. Prospectively, the Company will adjust the ROU assets for straight-line rent

expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has lease agreements with lease and non-lease components, which are accounted for as a combined element.

Deferred Offering Costs

The Company capitalizes certain legal, professional, accounting and other third-party fees that are directly associated with in process equity financings as deferred offering costs until the related financings are consummated. After consummation of the equity financing, such costs are reclassified as a reduction to additional paid-in capital generated as a result of the related financing. Should an in-process equity financing be abandoned, the deferred offering costs will be expensed immediately and accounted for as operating expenses in the consolidated statements of operations and comprehensive loss. Deferred offering costs are presented as a component of other current assets on the condensed consolidated balance sheets.

Research and Development Costs and Accruals

Research and development expenses are expensed as incurred and consist of costs incurred in performing research and development activities, including compensation related expenses for research and development personnel, preclinical and clinical activities including cost of supply and manufacturing process development activities, overhead expenses including facilities expenses, materials and supplies, amounts paid to consultants and outside service providers, and depreciation of equipment. Upfront payments made for the licensing of technology are expensed as research and development expenses in the period in which they are incurred. In general, contingent payments are recognized when it becomes probable the payment will be required. Any contingent payments that qualify as a derivative liability are recognized at fair value on the Company's consolidated balance sheets. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

The Company records accruals for estimated ongoing research and development costs, including costs associated with contracts with third-party contract research organizations and contract manufacturing organizations. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the preclinical studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Acquired In-Process Research and Development ("IPR&D")

If the Company acquires an asset or group of assets under an in-licensing arrangement that does not meet the definition of a business under ASC Topic 805, *Business Combinations*, and the acquired IPR&D does not have an alternative future use, it is expensed on its acquisition date in accordance with guidance in ASC Topic 730, *Research and Development*. Contingent payments for the assets acquired are expensed or capitalized based on the nature of the associated asset at the date the payment is recognized.

Patent Costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the accompanying consolidated statements of operations and comprehensive loss.

Equity-Based Compensation

The Company issues equity-based awards to employees, directors and non-employees, generally in the form of stock options. The Company measures employee equity-based compensation based on the grant date fair value of the equity-based awards and recognizes equity-based compensation expense on a straight-line basis over the requisite service period of the awards, which is generally the vesting period of the respective award, in accordance with ASC 718, *Compensation—*

Stock Compensation ("Topic 718"). Topic 718 requires all equity-based payments to employees, which includes grants of employee equity awards, to be recognized in the consolidated statements of operations and comprehensive loss based on their grant date fair values.

There are significant judgments and estimates inherent in the determination of the fair value of the common securities. The Company considers the fair value of common stock to be equal to its current share price. If applicable, the current share price is adjusted to reflect material nonpublic information known to the company but unavailable to market participants. Prior to the completion of the Company's IPO, the Company determined the fair value of the underlying common stock based on input from management and approved by the Company's board of directors, which utilized the valuation of the Company's enterprise value determined utilizing various methods including the market adjusted equity value method, guideline initial public offering method, transactions method, recent transactions method, option-pricing method, or a hybrid method. The total enterprise value was then allocated to the various outstanding equity instruments, including the underlying common stock, utilizing the option-pricing method.

The Company estimates the fair value of stock options using the Black-Scholes option pricing model, which uses as inputs the estimated fair value of common stock, and certain management estimates, including the expected stock price volatility, the expected term of the award, the risk-free rate, and expected dividends. Expected volatility is calculated based on reported volatility data for a representative group of publicly traded companies for which historical information is available. The Company selects companies with comparable characteristics with historical share price information that approximates the expected term of the equity-based awards. The Company computes the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period that approximates the calculated expected term of the stock options. The Company will continue to apply this method until a sufficient amount of historical information regarding the volatility of its stock price becomes available. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption. The Company uses the simplified method, under which the expected term is presumed to be the midpoint between the vesting date and the end of the contractual term. The Company utilizes this method due to lack of historical exercise data and the plain nature of its equity-based awards. The expected dividend yield is assumed to be zero as the Company has no current plans to pay any dividends on common stock.

For awards with service-based vesting conditions, the Company recognizes equity-based compensation expense on a ratable basis over the vesting period. For awards subject to performance conditions, the Company recognizes equity-based compensation expense using an accelerated recognition method over the remaining service period when the Company determines the achievement of the performance condition is probable. The Company uses judgement to determine whether and, if so, how many awards are deemed probable of vesting at each reporting period. The Company recognizes forfeitures as they occur. The Company classifies equity-based compensation expense in its consolidated statements of operations and comprehensive loss consistent with the classification of the award recipient's salary and related costs or the award recipient's service payments, as applicable.

Convertible Preferred Stock

Prior to the automatic conversion of all outstanding shares of the Company's convertible preferred stock upon the closing of the IPO, the Company recorded all shares of convertible preferred stock at their respective fair values on the dates of issuance less issuance costs. The Company classified its convertible preferred stock outside of stockholders' equity (deficit) when the redemption of such shares was outside the Company's control. The Company did not adjust the carrying values of the convertible preferred stock to the liquidation preferences of such stock until such time as a deemed liquidation event was probable of occurring.

Comprehensive Loss

Comprehensive loss is the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss includes net loss and the change in accumulated other comprehensive loss for the period. The Company did not have any items of comprehensive income or loss other than net loss for the years ended December 31, 2022 and 2021.

Net Loss Per Share

The Company applies the two-class method to compute basic and diluted net loss per share because it has issued shares that meet the definition of participating securities. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires losses available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to share in the earnings as if all losses for the period had been distributed. During periods of loss, there is no allocation required under the two-class method since the participating securities do not have a contractual obligation to fund the losses of the Company.

The Company calculates basic net loss per share attributable to common stockholders by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, which excludes shares of restricted common stock that are not vested. Diluted net loss per share is calculated by dividing net loss by the weighted average number of shares of common stock outstanding, as applicable, after giving consideration to the dilutive effect of preferred units, convertible preferred stock, incentive units, stock options, restricted common stock and warrants that are outstanding during the period. The Company has generated a net loss in all periods presented, so the basic and diluted net loss per share are the same, as the inclusion of the potentially dilutive securities would be anti-dilutive.

Income Taxes

Income taxes for Xilio Therapeutics, Inc. are recorded in accordance with ASC Topic 740, *Income Taxes*, which provides for deferred taxes using an asset and liability approach. Under this method, deferred income tax assets and liabilities are recognized based on future income tax consequences attributable to differences between the financial statement carrying amount of existing assets and liabilities, and their respective income tax basis. Deferred income tax assets and liabilities are measured using enacted income tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect of changes in income tax rates on deferred income tax assets and liabilities is recognized as income or expense in the period that includes the enactment date and subject to a valuation allowance which is established for any income tax benefits of which future realization is not more likely than not.

The Company provides reserves for potential payments of tax to various tax authorities related to uncertain tax positions. The tax benefits recorded are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is "more likely than not" to be realized following resolution of any uncertainty related to the tax benefit, assuming that the matter in question will be raised by the tax authorities. At December 31, 2022 and 2021, the Company had not identified any significant uncertain tax positions.

Recently Adopted Accounting Pronouncements

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326)—Measurement of Credit Losses on Financial Instruments*, as amended ("ASU 2016-13"). The provisions of ASU 2016-13 modify the impairment model to utilize an expected loss methodology in place of the previously used incurred loss methodology and require a consideration of a broader range of reasonable and supportable information to inform credit loss estimates. The Company adopted ASU 2016-13 as of January 1, 2022, and the adoption did not have a material effect on its consolidated financial statements and related disclosures.

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging Contracts in Entity's Own Equity (Subtopic 815-40)* ("ASU 2020-06"), which reduces the number of accounting models for convertible debt instruments and convertible preferred stock as well as amends the derivatives scope exception for contracts in an entity's own equity. The Company adopted ASU 2020-06 as of January 1, 2022, and the adoption did not have a material effect on its consolidated financial statements and related disclosures.

3. Fair Value Measurements

The Company measures the following financial assets and liabilities at fair value on a recurring basis. The fair value of these assets and liabilities was determined as follows (in thousands):

	December 31, 2022	Quoted Prices in Active Markets for Identical Assets Level 1	Significant Other Observable Inputs Level 2	Significant Unobservable Inputs Level 3
Financial assets:				
Cash equivalents—money market funds	$ 939	$ 939	$ —	$ —
Total financial assets	$ 939	$ 939	$ —	$ —

	December 31, 2021	Quoted Prices in Active Markets for Identical Assets Level 1	Significant Other Observable Inputs Level 2	Significant Unobservable Inputs Level 3
Financial assets:				
Cash equivalents—money market funds	$ 8,534	$ 8,534	$ —	$ —
Total financial assets	$ 8,534	$ 8,534	$ —	$ —

During the years ended December 31, 2022 and 2021, the Company did not hold any investments and there were no transfers between Level 1, Level 2 and Level 3.

In May 2016, the Company issued to a consultant a warrant to purchase 25,000 Series A preferred units at a price of $1.00 per unit, and in June 2020, the preferred unit warrant was converted into a warrant to purchase 25,000 shares of Series A convertible preferred stock at a price of $1.00 per share. The fair value of the warrant liability utilized the Black-Scholes option-pricing model which incorporated significant inputs not observable in the market, and thus represented a Level 3 measurement within the fair value hierarchy. Based on the terms and conditions of the warrant, upon the completion of the Company's IPO the warrant to purchase 25,000 shares of Series A convertible preferred stock automatically became a warrant to purchase 2,631 shares of common stock. Upon conversion into a warrant to purchase common stock, the Company concluded that the warrant met the definition of an equity instrument and the fair value of the warrant at the time of conversion, determined using the Black-Scholes option pricing model, was reclassified from other liabilities, long-term to additional paid-in capital.

The fair values of the debt derivative liability and the other derivative liability that were contingently payable upon the consummation of specified transactions, including an initial public offering, were based on significant inputs not observable in the market, including estimates regarding the probability of certain potential future events and outcomes and estimates regarding timing of those events and outcomes, with an applied discount rate representative of time value that represents a Level 3 measurement within the fair value hierarchy. The debt derivative liability and other derivative liability were paid during the year ended December 31, 2021 subsequent to the completion of the Company's IPO. Accordingly, there was no amount recorded for the debt derivative liability and other derivative liability in the Company's consolidated balance sheets as of December 31, 2022 and 2021.

The following table summarizes the changes in the fair market value of the Company's warrant liability, debt derivative liability and other derivative liability, which are classified within the Level 3 fair value hierarchy (in thousands):

	Warrant liability	Debt derivative liability	Other derivative liability	Total level 3 financial liabilities
Balance at December 31, 2020	$ 22	$ 396	$ 407	$ 825
Change in fair value of liability	6	354	93	453
Settlement of liability	—	(750)	(500)	(1,250)
Conversion of warrant liability to equity upon initial public offering	(28)	—	—	(28)
Balance at December 31, 2021	$ —	$ —	$ —	$ —

4. Property and Equipment, Net

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

	December 31, 2022	December 31, 2021
Laboratory equipment	$ 5,587	$ 3,805
Computers and software	228	228
Furniture and fixtures	636	636
Leasehold improvements	5,124	5,124
Construction in process	98	539
Total property and equipment	$ 11,673	$ 10,332
Less: accumulated depreciation	(4,418)	(2,712)
Property and equipment, net	$ 7,255	$ 7,620

The Company incurred depreciation and amortization expense related to property and equipment of $1.7 million and $1.4 million for the years ended December 31, 2022 and 2021, respectively.

5. Accrued Expenses

Accrued expenses consist of the following as of December 31, 2022 and 2021 (in thousands):

	December 31, 2022	December 31, 2021
External research and development	$ 3,178	$ 2,794
Personnel-related	5,413	5,145
Professional and consulting fees	1,536	491
Other	200	321
Total accrued expenses	$ 10,327	$ 8,751

6. Loan and Security Agreement

In November 2019, the Company entered into a loan and security agreement (as amended, the "Loan Agreement") with Pacific Western Bank ("PacWest"), pursuant to which the Company borrowed $10.0 million under a term loan. Interest on amounts outstanding under the Loan Agreement accrue at a variable annual rate equal to the greater of (i) the prime rate plus 0.25% or (ii) 4.75%. As of December 31, 2022, the interest rate on the term loan is 7.75%. The Company was required to make interest-only payments on any outstanding balances through December 31, 2022. The Company commenced making equal monthly payments of principal plus interest in January 2023, and it will be required to make such payments until the term loan matures on June 30, 2024. In addition, under the Loan Agreement, the Company paid a one-time success fee of $0.8 million to PacWest in the fourth quarter of 2021 upon the closing of the IPO.

The Loan Agreement contains customary representations, warranties and covenants and also includes customary terms covering events of default, including payment defaults, breaches of covenants, a change of control provision and occurrence of a material adverse effect. As security for its obligations under the Loan Agreement, the Company granted PacWest a first priority security interest on substantially all of the Company's assets (other than intellectual property), subject to certain exceptions.

The Company has determined that the risk of subjective acceleration under the material adverse effect clause is not probable and therefore has classified the long-term portion of the outstanding principal in non-current liabilities. Upon the occurrence and continuation of an event of default, a default interest rate of an additional 5% per annum may be applied to the outstanding loan balance, and the administrative agent, collateral agent, and lender may declare all outstanding obligations immediately due and payable and exercise all of their rights and remedies as set forth in the Loan Agreement and under applicable law. As of December 31, 2022, the Company was in compliance with all covenants under the Loan Agreement.

The Company has the following minimum aggregate future loan payments under the Loan Agreement at December 31, 2022 (in thousands):

	Minimum Loan Payments
2023	$ 6,667
2024	3,333
Total future principal payments	10,000
Less: unamortized discount	(168)
Total notes payable	$ 9,832

The Company recognized $0.8 million and $0.6 million of interest expense related to the Loan Agreement for the years ended December 31, 2022 and 2021, respectively, which is reflected in other income (expense), net on the consolidated statements of operations and comprehensive loss.

7. Intellectual Property Licenses

Cross-License Agreement with AskGene

In December 2020, Xilio Development entered into a cross-license agreement with AskGene Pharma, Inc. ("AskGene") pursuant to which AskGene granted Xilio Development certain exclusive licenses for AskGene patent rights related to non-antigen binding IL-2 products in the field of oncology and certain co-exclusive licenses for AskGene patent rights related to antigen binding IL-2 products in all fields. Under the agreement, AskGene retains rights to the AskGene patent rights in Singapore, Thailand, Malaysia, Vietnam, the People's Republic of China, Taiwan, Macau, Hong Kong, Korea and India (the "AskGene territory"), and granted licenses to Xilio Development for the AskGene patent rights worldwide, excluding the AskGene territory (the "Xilio Development territory").

Under the agreement, Xilio Development paid AskGene an upfront payment of $6.0 million, and for any licensed IL-2 product, Xilio Development is obligated to pay AskGene up to $13.0 million in the aggregate upon the achievement of specified regulatory milestones. In addition, subject to specified conditions, for any IL-2 licensed product, Xilio Development is obligated to pay AskGene percentage royalties in the mid-single digits on aggregate annual net sales of IL-2 licensed products in the Xilio Development territory during the applicable royalty term.

During the term of the agreement, AskGene has agreed not to exploit any non-antigen binding IL-2 product comprised of specified masking technology in the field of oncology in the Xilio Development territory.

In addition, Xilio Development granted a non-exclusive, royalty-free, non-transferable, worldwide license to AskGene for specified Xilio patent rights related to non-antigen binding IL-2 products in the field of immunology and for specified Xilio patent rights related to antigen binding IL-2 products in all fields. Subject to the terms of the agreement and during the time period specified, Xilio Development also granted AskGene an option to obtain a license in the AskGene territory

to develop and commercialize IL-2 licensed products. If AskGene exercises its option to develop and commercialize IL-2 licensed products in the AskGene territory, then the parties will negotiate and enter into a license agreement for AskGene's exclusive development and commercialization of such products in the AskGene territory, and AskGene would be obligated to pay Xilio Development percentage royalties in the mid-single digits on aggregate annual net sales of such licensed products in the AskGene territory.

The Company accounted for the agreement as an asset acquisition, as the Company only acquired licenses to specified patents from AskGene (an input) and no additional processes or outputs as a part of the agreement. The $6.0 million upfront payment was recorded as research and development expense in the consolidated statement of operations and comprehensive loss during the year ended December 31, 2020, as the acquired licenses were determined to have no alternative future use and the technological feasibility of the intellectual property has not yet been reached. Any additional payments that are contingent upon achievement of development and regulatory milestones or upon sales of licensed products will not be recognized until it becomes probable that the Company will be required to make such payments.

Amended and Restated Exclusive License Agreement with City of Hope

In August 2016, Xilio Development entered into an amended and restated exclusive license agreement with City of Hope pursuant to which City of Hope granted Xilio Development an exclusive worldwide license to specified patent rights related to the Company's anti-CTLA-4 monoclonal antibody program.

Under the agreement, the Company issued 24,019 shares of common stock to City of Hope. For the first three licensed products or licensed services to achieve specified development and regulatory milestones, Xilio Development is obligated to pay City of Hope up to $10.3 million in the aggregate per licensed product or licensed service. In addition, subject to specified conditions, Xilio Development is obligated to pay City of Hope tiered royalties in the low single digits on aggregate annual net sales of licensed products or licensed services on a country-by-country basis until the expiration of the last-to-expire patent or patent application licensed from City of Hope covering the applicable licensed product or licensed service in such country. Xilio Development is also obligated to pay City of Hope a portion of any consideration Xilio Development receives for the grant of sublicenses under the agreement ranging from a low double digit to mid-twenties percentage of such consideration, subject to specified conditions under that agreement at the time that Xilio Development grants any such sublicense.

The Company incurred no costs related to the payment of specified development milestones under the agreement during the year ended December 31, 2022. The Company incurred $0.3 million in costs related to the payment of specified development milestones under the agreement during the year ended December 31, 2021. In each of the years ended December 31, 2022 and 2021, the Company incurred $10,000 under this agreement, which was recognized as research and development expense in the consolidated statements of operations and comprehensive loss. Any additional payments that are contingent upon achievement of development and regulatory milestones or upon sales of licensed products will not be recognized until it becomes probable that the Company will be required to make such payments.

CTLA-4 Monoclonal Antibody License Agreement with WuXi Biologics

In September 2016, the Company entered into a license agreement with WuXi Biologics (Hong Kong) Limited ("WuXi Biologics"), as amended in December 2017, pursuant to which WuXi Biologics granted the Company an exclusive worldwide license to specified monoclonal antibodies and patent rights and know-how controlled by WuXi Biologics, including certain patent rights related to the Company's anti-CTLA-4 monoclonal antibody program.

For each product that exploits the rights licensed under the agreement, the Company is obligated to pay WuXi Biologics up to approximately $25.8 million in the aggregate for specified development and regulatory milestones. In addition, subject to specified conditions, the Company is obligated to pay WuXi Biologics tiered royalties in the low to mid-single digits on aggregate annual worldwide net sales of licensed products during the applicable royalty term.

The Company incurred no costs related to the payment of specified development milestones under the agreement during the year ended December 31, 2022. The Company incurred $0.8 million in costs related to the payment of specified development milestones under the agreement during the year ended December 31, 2021. Any additional payments that are

contingent upon the achievement of development and regulatory milestones or sales of licensed products will not be recognized until it becomes probable that the Company will be required to make such payments.

8. Leases

The Company has an operating lease for its headquarters and a finance lease for certain lab equipment. In August 2019, the Company entered into a facility lease agreement with a landlord providing funding for tenant improvements and occupancy of approximately 27,830 square feet of office and laboratory space (the "premises") at 828 Winter Street, Waltham, Massachusetts. The initial term of the lease expires in March 2030, unless terminated earlier in accordance with the terms of the lease. The Company has a right to a five-year option to extend at then-market rates. The Company is obligated to pay its portion of real estate taxes and costs related to the premises, including costs of operations, maintenance, repair, replacement, and management of the leased premises, which it began paying simultaneous with the rent commencement date in March 2020. As of December 31, 2022 and 2021, the Company has a letter of credit for the benefit of its landlord in the amount of $1.6 million, collateralized by a money market fund, which is recorded as restricted cash on the consolidated balance sheets.

The components of lease expense were as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Operating lease cost	$ 1,225	$ 1,225
Variable lease cost	959	772
Total lease costs	$ 2,184	$ 1,997
Finance lease cost:		
Amortization of right-of-use asset	$ 85	$ 85
Interest on lease liability	12	16

Supplemental balance sheet information related to the leases was as follows (in thousands, except for remaining lease term and discount rates):

	Year Ended December 31,	
	2022	2021
Operating Lease:		
Operating lease right-of-use asset	$ 5,585	$ 5,977
Operating lease liability, current portion	$ 918	$ 801
Operating lease liability, net of current portion	$ 9,189	$ 10,107
Finance Lease:		
Other non-current assets	$ 219	$ 303
Other current liabilities	82	82
Other liabilities, long-term	45	118
Weighted-average remaining lease term (in years):		
Operating lease	7.17	8.17
Finance lease	1.70	2.70
Weighted-average discount rate:		
Operating lease	8.0 %	8.0 %
Finance lease	6.9 %	6.9 %

Supplemental cash flow information related to leases was as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Cash paid for amounts included in the measurement of lease liabilities:		
Operating cash flows from operating leases	$ 1,634	$ 1,392
Financing cash flows from finance leases	85	85

Future minimum lease payments under non-cancellable leases as of December 31, 2022 are as follows (in thousands):

	Operating Lease	Finance Lease
2023	$ 1,683	$ 85
2024	1,733	49
2025	1,785	—
2026	1,839	—
2027	1,894	—
Thereafter	4,467	—
Total future minimum lease payments	$ 13,401	$ 134
Present value adjustment	(3,294)	(7)
Present value of lease liabilities	$ 10,107	$ 127

9. Commitments and Contingencies

Indemnification Agreements

In the ordinary course of business, the Company enters into agreements that may include indemnification provisions. Pursuant to such agreements, the Company may indemnify, hold harmless and defend an indemnified party for losses suffered or incurred by the indemnified party. Some of the provisions will limit losses to those arising from third-party actions. In some cases, the indemnification will continue after the termination of the agreement. The maximum potential amount of future payments the Company could be required to make under these provisions is not determinable. The Company has never incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. The Company has also entered into indemnification agreements with its directors that may require the Company to indemnify its directors against liabilities that may arise by reason of their status or service as directors to the fullest extent permitted by Delaware corporate law. The Company currently has directors' and officers' liability insurance.

To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2022 or 2021.

Legal Proceedings

The Company is not currently a party to any material legal proceedings.

10. Preferred Stock and Common Stock

Undesignated Preferred Stock

On October 26, 2021, in connection with the closing of the Company's IPO, the Company amended and restated its Certificate of Incorporation authorizing the Company to issue 5,000,000 shares of undesignated preferred stock at $0.0001 par value per share.

Convertible Preferred Stock

Upon the closing of the IPO in October 2021, all shares of the Company's then outstanding convertible preferred stock automatically converted into an aggregate of 18,398,248 shares of common stock. There was no convertible preferred stock outstanding as of December 31, 2022 and 2021.

Common Stock

As of December 31, 2022 and 2021, the Company's certificate of incorporation, as amended, authorized the Company to issue up to 200,000,000 shares of common stock, $0.0001 par value per share.

On November 9, 2022, the Company filed a registration statement on Form S-3 (the "2022 Shelf Registration Statement"), covering the offering of up to $250.0 million of common stock, preferred stock, debt securities, units and warrants. The 2022 Shelf Registration Statement became effective on November 18, 2022.

On November 9, 2022, the Company also entered into a Sales Agreement (the "Sales Agreement") with Cowen and Company, LLC ("Cowen"), under which the Company may, from time to time, sell shares of its common stock through Cowen (the "2022 ATM Program"). The 2022 Shelf Registration Statement included a prospectus covering the offering, issuance and sale of up to $75.0 million of the Company's common stock from time to time through the 2022 ATM Program. Through December 31, 2022, the Company has not sold any common stock through the 2022 ATM Program.

The voting, dividend and liquidation rights of the holders of shares of common stock are subject to and qualified by the rights, powers and preferences of the holders of shares of the Company's undesignated preferred stock, if and when such shares are issued. The rights, preferences and privileges of the Company's common stock are as follows:

Voting

The holders of shares of common stock are entitled to one vote for each share of common stock held at any meeting of stockholders and at the time of any written action in lieu of a meeting of stockholders.

Dividends

The holders of shares of common stock are entitled to receive dividends, if and when declared by the Company's board of directors. No dividends have been declared by the Company's board of directors or paid by the Company to the holders of common stock since the issuance of the common stock.

Liquidation

Upon the dissolution, liquidation or winding up of the Company, whether voluntary or involuntary, holders of the common stock will be entitled to receive, pro rata based on the number of shares held by each such holder, all assets of the Company available for distribution to its stockholders, subject to any preferential or other rights of any then outstanding preferred stock.

Shares Reserved for Future Issuance

As of December 31, 2022 and 2021, the Company had reserved shares of common stock for future issuance under the 2020 Stock Incentive Plan (as amended, the "2020 Plan"), the 2021 Stock Incentive Plan (the "2021 Plan"), the 2021

Employee Stock Purchase Plan (the "2021 ESPP") and the 2022 Inducement Stock Incentive Plan (the "2022 Inducement Plan") as follows:

	December 31, 2022	December 31, 2021
Shares of common stock reserved for exercise of a warrant	2,631	2,631
Shares of common stock reserved for exercise of outstanding stock options under the 2021 and 2020 Stock Incentive Plans	4,960,553	4,088,456
Shares of common stock reserved for future awards under the 2021 Stock Incentive Plan	2,848,568	2,349,875
Shares of common stock reserved for purchase under the 2021 Employee Stock Purchase Plan	566,720	292,031
Shares of common stock reserved for future awards under the 2022 Inducement Plan	275,000	—
Total shares reserved for future issuance	8,653,472	6,732,993

11. Equity-Based Compensation

Equity Incentive Plans

2020 Stock Incentive Plan

In July 2020, the Company's stockholders approved the 2020 Plan. Under the 2020 Plan, the Company was authorized to issue shares of common stock to the Company's employees, officers, directors, consultants, and advisors in the form of options, restricted stock awards or other stock-based awards. Upon the effectiveness of the 2021 Plan in October 2021, the Company ceased granting awards under the 2020 Plan.

2021 Stock Incentive Plan

In September 2021, the Company's board of directors adopted the 2021 Plan, which was approved by the Company's stockholders and became effective immediately prior to the effectiveness of the Company's registration statement on Form S-1, as amended (File No. 333-259973), which was declared effective by the SEC on October 21, 2021 (the "Registration Statement"). The 2021 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units, and other stock-based awards. The number of shares of the Company's common stock initially reserved for issuance under the 2021 Plan was the sum of (1) 2,654,828; plus (2) the number of shares (up to 3,967,038 shares) as is equal to the sum of (x) the number of shares of the Company's common stock reserved for issuance under the 2020 Plan that remained available for grant under the 2020 Plan immediately prior to the effectiveness of the Registration Statement and (y) the number of shares of the Company's common stock subject to outstanding awards whether granted under the 2020 Plan or outside of the 2020 Plan which awards expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right and that, prior to the effectiveness of the 2021 Plan, would have become available for issuance under the 2020 Plan; plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year, commencing on January 1, 2022 and continuing until, and including, January 1, 2031, equal to the lesser of (i) 5% of the number of shares of the Company's common stock outstanding on the first day of such fiscal year and (ii) the number of shares of common stock determined by the Company's board of directors (the "Evergreen Provision"). Effective January 1, 2023, the number of shares reserved for issuance under the 2021 Plan increased by 1,373,580 shares in accordance with the Evergreen Provision.

As of December 31, 2022, there were 2,848,568 shares available for future issuance under the 2021 Plan.

2021 Employee Stock Purchase Plan

In September 2021, the Company's board of directors adopted, and in October 2021, the Company's stockholders approved the 2021 ESPP, which became effective on October 21, 2021, immediately prior to the effectiveness of the Registration Statement. The 2021 ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 292,031 shares of the Company's common stock. The number of shares of common stock reserved for issuance under the 2021 ESPP will automatically increase on each January 1, beginning on January 1, 2022 and ending on January 1, 2031, by the lesser of (i) 584,062 shares of common stock, (ii) 1% of the number of shares of the Company's common stock outstanding on such date, and (iii) a number of shares of common stock as determined by the Company's board of directors. Effective January 1, 2023, the number of shares reserved for issuance under the 2021 ESPP increased by 274,716 shares. The first offering period under the 2021 ESPP commenced on December 1, 2022 and ends May 31, 2023. As of December 31, 2022, no shares have been issued under the 2021 ESPP.

As of December 31, 2022, there were 566,720 shares available for future issuance under the 2021 ESPP.

2022 Inducement Plan

On November 18, 2022, the Company's board of directors adopted the 2022 Inducement Plan pursuant to Nasdaq Rule 5635(c)(4). In accordance with Rule 5635(c)(4), cash and equity-based incentive awards under the 2022 Inducement Plan may only be made to a newly hired employee who has not previously been a member of the Company's board of directors, or an employee who is being rehired following a bona fide period of non-employment by the Company as a material inducement to the employee's entering into employment with the Company. An aggregate of 275,000 shares of the Company's common stock has been reserved for issuance under the 2022 Inducement Plan.

The exercise price of stock options granted under the 2022 Inducement Plan will not be less than the fair market value of a share of the Company's common stock on the grant date. Other terms of awards, including vesting requirements, are determined by the Company's board of directors and are subject to the provisions of the 2022 Inducement Plan. As of December 31, 2022, no shares have been granted under the 2022 Inducement Plan.

Total Equity-Based Compensation Expense

During the years ended December 31, 2022 and 2021, the Company recorded compensation expense related to stock options and restricted common stock for employees and non-employees, which was allocated as follows in the consolidated statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development expense	$ 2,427	$ 1,290
General and administrative expense	5,997	3,668
Total equity-based compensation expense	$ 8,424	$ 4,958

Stock Options

A summary of stock option activity under the Company's Stock Incentive Plans is as follows:

	Number of Stock Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (In years)	Aggregate Intrinsic Value (1) (In thousands)
Outstanding as of December 31, 2021	4,088,456	$ 8.59	9.13	$ 30,291
Granted	1,745,366	$ 7.93		
Exercised	(2,657)	$ 5.89		
Cancelled/forfeited	(870,612)	$ 10.39		
Outstanding as of December 31, 2022	4,960,553	$ 8.04	8.59	$ 89
Exercisable as of December 31, 2022	1,727,063	$ 7.85	8.20	$ 4
Vested and expected to vest as of December 31, 2022	4,960,553	$ 8.04	8.59	$ 89

(1) The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock as of the end of the period.

Using the Black-Scholes option pricing model, the weighted average fair value of options granted to employees and directors during the years ended December 31, 2022 and 2021 was $5.58 per share and $6.28 per share, respectively. The Company satisfies stock option exercises with newly issued shares of common stock. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2022 and 2021 was less than $0.1 million and $0.5 million, respectively.

The following assumptions were used in determining the fair value of options granted to employees during the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
Risk-free interest rate	1.47 – 4.22 %	0.63 – 1.39 %
Expected dividend yield	0 %	0 %
Expected term (in years)	5.27 – 6.08	5.52 – 10.00
Expected volatility	80.75 – 87.64 %	80.55 – 85.26 %

As of December 31, 2022, the Company had unrecognized equity-based compensation expense of $16.8 million related to stock options issued to employees and directors, which is expected to be recognized over a weighted average period of 2.58 years.

Restricted Stock

A summary of the Company's restricted stock activity and related information is as follows:

	Number of Shares of Restricted Stock	Weighted Average Grant Date Fair Value
Unvested as of December 31, 2021	110,575	$ 5.51
Vested	(64,415)	$ 5.51
Canceled/Forfeited	—	$ —
Unvested as of December 31, 2022	46,160	$ 5.51

In June 2020, the Company granted 552,546 shares of common stock underlying restricted stock awards, and the Company has not subsequently granted any additional restricted stock awards. The Company recorded equity-based compensation expense for restricted stock granted to employees, directors and non-employees of $0.4 million and $0.5 million for the years ended December 31, 2022 and 2021, respectively. During the years ended December 31, 2022 and 2021, the aggregate fair value of the restricted stock awards that vested was $0.3 million and $1.0 million, respectively. As of December 31, 2022, total unrecognized compensation cost related to unvested restricted stock awards was approximately $0.3 million, which is expected to be recognized over a weighted-average period of 0.94 years.

12. Net Loss Per Share

The following table sets forth the outstanding common stock equivalents, presented based on amounts outstanding at each period end, that were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have been anti-dilutive.

	Year Ended December 31,	
	2022	2021
Unvested restricted common stock	46,160	110,575
Outstanding stock options	4,960,553	4,088,456
Warrants	2,631	2,631
Unvested employee stock purchase plan shares	77,222	—
Total common stock equivalents	5,086,566	4,201,662

13. Income Taxes

The Company has not recorded a current or deferred tax provision for the years ended December 31, 2022 and 2021. The effective income tax rate differed from the amount computed by applying the federal statutory rate to the Company's loss before income taxes as follows:

	Year Ended December 31,	
	2022	2021
Tax effected at statutory rate	21.0 %	21.0 %
State taxes	5.2	6.7
Equity-based compensation	(0.6)	(0.5)
Non-deductible expenses	(0.9)	(0.3)
Federal research and development credits	2.8	1.7
Change in valuation allowance	(27.5)	(28.6)
Effective income tax rate	0.0 %	0.0 %

Deferred tax assets consist of the following as of December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
Deferred tax assets:		
Federal net operating loss carryforwards	$ 37,277	$ 31,387
State net operating loss carryforwards	9,267	8,910
Research and development credit carryforwards	7,104	3,873
Capitalized research and development expenditures	14,469	—
Lease liability	2,761	2,980
Accruals and reserves	241	340
Intangible assets	1,917	2,061
Equity-based compensation	1,374	733
Total deferred tax assets:	74,410	50,284
Valuation allowance	(71,003)	(46,745)
Subtotal	3,407	3,539
Deferred tax liabilities:		
Property and equipment	(1,881)	(1,883)
Right of use asset	(1,526)	(1,633)
Debt discount	—	(23)
Total deferred tax liabilities	(3,407)	(3,539)
Net deferred tax assets	$ —	$ —

The Company has had no income tax expense due to operating losses incurred since inception. Deferred tax assets are reduced by a valuation allowance if, based on the weight of available positive and negative evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on this, the Company has provided a valuation allowance for the full amount of the net deferred tax assets as the realization of the deferred tax assets is not determined to be more likely than not. During the year ended December 31, 2022, the valuation allowance increased by $24.3 million primarily due to the increase in the Company's book loss reported in the period, capitalized research and development expenditures and the generation of additional research and development credits.

As of December 31, 2022, the Company had $177.5 million and $146.6 million of federal and state operating loss carryforwards, respectively. Of the federal net operating loss carryovers, $172.7 million are not subject to expiration and the remaining federal and state net operating loss carryovers begin to expire in 2035. These loss carryforwards are available to reduce future federal taxable income, if any. As of December 31, 2022, the Company had $5.2 million and $2.5 million of federal and state credit carryovers which begin to expire in 2033. These loss and credit carryforwards are subject to review and possible adjustment by the appropriate taxing authorities.

Utilization of the Company's net operating loss ("NOL") carryforwards and research and development credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future in accordance with Section 382 of the Internal Revenue Code of 1986, as amended ("Section 382") as well as similar state provisions. These ownership changes may limit the amount of NOL and research and development credit carryforwards that can be utilized annually to offset future taxable income and taxes, respectively. In general, an ownership change as defined by Section 382 results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. Since its formation, the Company has raised capital through the issuance of capital stock on several occasions. These financings could result in a change of control as defined by Section 382. The Company has not yet completed a detailed study of its inception to date ownership change activity.

The Company follows the provisions of ASC 740-10, *Accounting for Uncertainty in Income Taxes*, which specifies how tax benefits for uncertain tax positions are to be recognized, measured, and recorded in financial statements; requires certain disclosures of uncertain tax matters; specifies how reserves for uncertain tax positions should be classified on the balance sheet; and provides transition and interim period guidance, among other provisions. As of December 31, 2022,

and 2021, the Company has not recorded tax reserves associated with any unrecognized tax benefits. The Company's policy is to recognize interest and penalties accrued on any uncertain tax positions as a component of income tax expense, if any, in its statements of income. As of December 31, 2022, and 2021, the Company had no reserves for uncertain tax positions. For the years ended December 31, 2022 and 2021, no estimated interest or penalties were recognized on uncertain tax positions. The Company has not recorded any interest or penalties on any unrecognized tax benefits since its inception.

The Company has not conducted a study of its research and development credit carryforwards. This study may result in an adjustment to research and development credit carryforwards; however, until a study is completed, and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the consolidated balance sheets or statements of operations and comprehensive loss if an adjustment were required.

The 2017 Tax Cuts and Jobs Act ("TCJA") included a multitude of tax provisions, including several deferred changes that became effective for tax years ending after December 31, 2021. Included in the provisions was the TCJA's amendment to Section 174 of the Internal Revenue Code of 1986, as amended ("Section 174"), which now requires U.S.-based and non-U.S-based research and experimental expenditures to be capitalized and amortized over a period of five or 15 years, respectively, for amounts paid in tax years starting after December 31, 2021. Prior to the TCJA amendment, Section 174 allowed taxpayers to either immediately deduct research and experimental expenditures in the year paid or incurred. The Company has applied this required change in accounting method beginning in 2022.

The Company's tax returns remain open to examination by the Internal Revenue Service and the Commonwealth of Massachusetts for the years ended December 31, 2019 to December 31, 2021. In addition, the Company's tax carryover attributes such as net operating losses or credits from earlier periods are also subject to examination. The Company is currently not subject to any examinations by the Internal Revenue Service or any other tax authorities for any tax years.

14. 401(k) Plan

In 2018, the Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code, as amended, the Xilio Therapeutics, Inc. 401(k) Plan (the "401(k) Plan"). The 401(k) Plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis or post-tax basis, up to the maximum amount prescribed by statute. The Company incurred an expense related to contributions on behalf of employees of $0.3 million to the 401(k) Plan during the year ended December 31, 2022. The Company did not incur an expense related to contributions on behalf of employees to the 401(k) Plan during the year ended December 31, 2021.

SENIOR LEADERSHIP TEAM

RENÉ RUSSO, PHARM.D.
CHIEF EXECUTIVE OFFICER

MARTIN HUBER, M.D.
PRESIDENT AND HEAD OF R&D

ULI BIALUCHA, PH.D.
CHIEF SCIENTIFIC OFFICER

STACEY DAVIS
CHIEF BUSINESS OFFICER

CHRIS FRANKENFIELD
CHIEF LEGAL AND ADMINISTRATIVE OFFICER

BOARD OF DIRECTORS

RENÉ RUSSO, PHARM.D.

PAUL J. CLANCY
CHAIR OF THE BOARD
FORMER EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER AT ALEXION PHARMACEUTICALS, INC.

SARA BONSTEIN
CHIEF FINANCIAL OFFICER OF INSMED, INC.

DANIEL CURRAN, M.D.
SVP AND HEAD OF RARE GENETICS AND HEMATOLOGY THERAPEUTIC AREA UNIT AT TAKEDA PHARMACEUTICAL COMPANY LTD.

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CHIEF OPERATING OFFICER OF BLUEPRINT MEDICINES CORPORATION

YUAN XU, PH.D.
FORMER CHIEF EXECUTIVE OFFICER AT LEGEND BIOTECH CORPORATION

ANNUAL MEETING OF STOCKHOLDERS

The 2023 annual meeting of stockholders will be held on Thursday, June 8, 2023 at 4 p.m. EDT online at www.virtualshareholdermeeting.com/XLO2023.

INDEPENDENT AUDITORS
Ernst & Young LLP

SEC FORM 10-K
A copy of Xilio Therapeutics' Form 10-K filed with the Securities and Exchange Commission is available free of charge from the company's investor relations department by emailing investors@xiliotx.com or sending a written request to: Investor Relations, Xilio Therapeutics Inc., 828 Winter Street, Suite 300, Waltham, MA 02451.

THE TRANSFER AGENT
The transfer agent is responsible, among other things, for handling stockholder questions regarding address changes, duplicate mailings and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address: Computershare Trust Company, N.A., 250 Royall Street, Canton, MA 02021, www.computershare.com, +1800 962 4284.

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