

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**FORM 10-K**

(Mark One)

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

For the fiscal year ended December 31, 2023

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 001-39527

**PRELUDE THERAPEUTICS INCORPORATED**

(Exact name of Registrant as specified in its Charter)

**Delaware**

(State or other jurisdiction of  
incorporation or organization)

**175 Innovation Boulevard**

**Wilmington, Delaware**

(Address of principal executive offices)

**81-1384762**

(I.R.S. Employer  
Identification No.)

**19805**

(Zip Code)

**Registrant's telephone number, including area code: (302) 467-1280**

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value \$0.0001 per share	PRLD	The Nasdaq Stock Market LLC

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 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 (§232.405 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 whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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

Non-accelerated filer

Accelerated filer

Smaller reporting company

Emerging growth company

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

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

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

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

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES  NO

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately \$77.1 million as of the last business day of the registrant's most recently completed second fiscal quarter, based upon the closing sale price on The Nasdaq Stock Market LLC reported for such date. This excludes an aggregate of 37,666,916 shares of the registrant's common stock held as of such date by officers, directors and stockholders that the registrant has concluded are or were affiliates of the registrant. Exclusion of such shares should not be construed to indicate that the holder of any such shares possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

The number of shares of Registrant's Common Stock outstanding as of February 9, 2024 was 54,920,594.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2024 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2023 fiscal year pursuant to Regulation 14A and is incorporated by reference into Part III of this Report. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.



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## PART I

*This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. All statements other than statements of historical facts are "forward-looking statements" for purposes of these provisions, including those relating to future events or our future financial performance. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "could," "should," "potential," "likely," "projects," "continue," "will," "schedule," and "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on the Company's current expectations and projections about future events and various assumptions. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. All forward-looking statements included in this Annual Report on Form 10-K are based on information available to us on the date hereof, and we assume no obligation to update any such forward-looking statements. Our forward-looking statements can be affected by inaccurate assumptions we might make or by known or unknown risks, uncertainties and other factors. We discuss many of these risks, uncertainties and other factors in this Annual Report on Form 10-K in greater detail under the heading "Item 1A—Risk Factors." It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.*

### **Item 1. Business.**

#### **Overview**

Prelude Therapeutics Incorporated ("Prelude") is a clinical-stage fully integrated oncology company built on a foundation of drug discovery excellence to deliver novel precision cancer medicines to underserved patients. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our clinical development capabilities, we have built an efficient, fully-integrated drug discovery engine and the development expertise necessary to identify compelling biological targets and create new chemical entities, or NCEs, that we advance into clinical trials. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our steady progress in creating a wholly owned, internally developed pipeline. We also began work with our partner AbCellera Biologics, Inc. ("AbCellera") on an early-stage discovery program involving potent degraders as payloads for novel antibodies targeting tumor specific antigens. Since our inception in 2016, we have received clearance from the U.S. Food and Drug Administration, or the FDA, for multiple investigational new drug applications, or INDs, and successfully advanced several programs into clinical trials. In addition, we have other differentiated proprietary programs in various stages of preclinical development.

By focusing on developing molecules using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of multiple distinct programs including kinases, targeted protein degraders, and precision antibody drug conjugates. Our pipeline is designed to serve patients with high unmet medical need, where there are limited or no treatment options. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

The following table summarizes our product candidate pipeline:

PROGRAM	CANCER INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	Strategic Priorities
<b>SMARCA2</b> PRT3789 (IV)	Patients with SMARCA4 mutated NSCLC and other cancers				Drive to POC in 2024
<b>CDK9</b> PRT2527	Patients with B, T-cell malignancies and AML				Drive to POC in 2024
<b>SMARCA2</b> (Oral)	Patients with SMARCA4 mutated NSCLC and other cancers				Target IND 1H 2024
<b>SMARCA</b> (Precision ADC)	Solid Tumors & Heme Malignancies not addressed by selective SMARCA2 degraders				Advance a Precision ADC Program with SMARCA Payload
<b>New precision ADCs</b>	Solid Tumors Heme Malignancies				Continue to build Precision ADC platform with novel payloads
<b>Small Molecule Discovery</b>	Solid Tumors Heme Malignancies				Advance a first-in-class small molecule program for a biomarker selected cancer

We have several drug candidates in clinical development and our objective is to generate proof-of-concept clinical data to guide our future regulatory pathways to approval. Our SMARCA2 molecule is a unique, first-in-class protein degrader, targeting specific patient populations. Our CDK9 inhibitor is selective and potent, with a potentially superior safety profile over first-generation CDK9 inhibitors. Our next generation CDK4/6 inhibitor is specifically designed to be brain and tissue penetrant.

Our novel, first-in-class SMARCA2 degrader compounds and our potent, highly selective and potentially best-in-class CDK9 inhibitor represent our best opportunities for demonstrating clinical proof-of-concept in 2024 and advancing into potential Phase 2/3 registration studies. In 2023 we also announced a global partnership with AbCellera that will allow us to combine our small molecules and degraders expertise with their antibody expertise to develop precision antibody drug conjugates. We also intend to explore continued clinical development with external partners for our CDK4/6.

PRT3789 is a first-in-class, highly selective degrader of SMARCA2 protein, which along with SMARCA4, controls gene regulation through chromatin remodeling. Cancer cells with SMARCA4 mutations are dependent on SMARCA2 for their growth and survival and selectively degrading SMARCA2 induces cell death in cancer cells while sparing normal cells in preclinical models. PRT3789 has been shown to be efficacious and well tolerated in multiple preclinical models of SMARCA4 deleted/mutated cancers as monotherapy and in combination with standards of care therapies. We believe a selective SMARCA2 degrader has the potential to be of benefit in up to 10% of Non-Small Cell Lung cancer, or NSCLC, patients in the United States including many other tumor types with the SMARCA4 mutation.

Patients with SMARCA4 mutations or deletions have poor clinical outcomes and limited treatment options. Therefore, mutated or deleted SMARCA4 cancers provide a potential biomarker to select those patients most likely to respond to treatment with a highly selective SMARCA2 degrader.

PRT3789 is currently in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. To date, PRT3789 has completed the fifth dose escalation cohort and demonstrated selective, potent and dose dependent degradation of SMARCA2 with an acceptable safety profile. Based on PK/PD and safety data to date, the Company expects to conclude monotherapy dose escalation in the middle of 2024 and identify recommended phase 2 doses. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations has been initiated. Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in combination with docetaxel, evaluate efficacy, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into a registrational clinical trial. We expect to present initial data in the second half of 2024 from patients currently enrolled in the Phase 1 trial.

Our discovery team has identified a series of highly selective and orally bioavailable SMARCA2 degraders. The lead oral molecule, PRT7732, is currently in investigational new drug (IND) enabling studies and on track to enter Phase 1

clinical development in the second half of 2024. PRT7732 is structurally distinct from PRT3789 and in addition, may provide clinically meaningful differences, more patient-friendly dosing and may have utility in earlier lines of therapy.

As one of our first precision ADC programs, Prelude and our partner AbCellera began work on an early-stage discovery program involving potent degraders of the SMARCA family of proteins as payloads for novel antibodies targeting tumor specific antigens. Given the potent anti-tumor activity of these molecules in pre-clinical models of cancers beyond those targeted by our SMARCA2 selective degraders, we believe that these precision ADCs have the potential to extend the therapeutic utility of this class. The partnership includes up to five precision ADC targets. Under the terms of the agreement, Prelude and AbCellera will jointly discover, develop, and commercialize products emerging from the collaboration. AbCellera will lead manufacturing activities and Prelude will lead clinical development and global commercialization, subject to AbCellera's option to co-promote any resulting commercial products in the United States.

Our CDK9 candidate, PRT2527, is designed to be a potent and selective CDK9 inhibitor. We believe PRT2527 has the potential to avoid off-target toxicities, achieve substantial clinical activity and to become the best-in-class CDK9 inhibitor for hematologic malignancies.

In preclinical studies, PRT2527 was shown to reduce MCL1 and MYC protein levels and was highly active in preclinical models at well-tolerated doses. Our preclinical studies suggest that PRT2527 demonstrates high kinase selectivity and potency, providing opportunity for a wider therapeutic index compared to less selective CDK9 inhibitors, allowing for rapid development in combinations.

Preclinical data demonstrated that treatment with PRT2527 depleted oncogenic drivers with short half-lives, such as MYC and MCL1, and effectively induced apoptosis. PRT2527 treatment demonstrated robust efficacy in both hematological malignancies and solid tumor models with MYC dysregulation. Dose dependent increases in exposure and target engagement were observed as evidenced by MYC and MCL1 depletion to levels associated with tumor regression in preclinical models. PRT2527 has completed a Phase 1 multi-dose escalation study (NCT05159518) in patients with solid tumors. In this study, PRT2527 was shown to achieve high levels of target inhibition and the potential to be better tolerated than existing CDK9 inhibitors, specifically, managing neutropenia and an absence of meaningful gastrointestinal events or hepatotoxicity.

The observed dose-dependent downregulation of MYC and MCL1 mRNA expression, CDK9 transcriptional targets, was consistent with the degree of target engagement required for preclinical efficacy. As predicted by the preclinical models, 12 mg/m<sup>2</sup> QW dosing showed optimal target inhibition and has been selected as the optimal dose. The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530). In this study, PRT2527 is advancing in monotherapy hematological indications, such as B-cell malignancies and acute myeloid leukemia (AML), and it has initiated the combination with zanubrutinib in B-cell malignancies. We expect to complete the monotherapy dose escalation in B-cell malignancies in the middle of 2024. A second cohort of patients with AML is expected to initiate in the first half of 2024 in monotherapy.

Our MCL1 candidate, PRT1419, was designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. We concluded Phase 1 development of PRT1419 and established a confirmation dose in hematological malignancies. Based on the potential to address the intended patient population with the CDK9 inhibitor which potently inhibits MCL-1, we decided to prioritize our CDK9 inhibitor, PRT2527, and to discontinue development of PRT1419.

PRT3645 is a brain and tissue penetrant molecule that potently targets CDK4/6 with a biased selectivity for CDK4. A Phase 1 multi-dose escalation clinical trial of PRT3645 is underway with the objective of establishing a biologically active dose confirmation. At the 2023 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, we presented data, showing that treatment with PRT3645 was associated with a substantial decrease in pRb and Ki67 expression, indicating a high level of target engagement at the doses evaluated. Also, PRT3645 was generally well tolerated in the initial three dose cohorts of patients with no clinically meaningful gastrointestinal, hematologic or neurological events reported to date, leveraging its enhanced selectivity profile. We intend to complete the dose escalation portion of the Phase 1 clinical trial of PRT3645 this year and following its completion, to explore continued clinical development with external partners.

## Prelude Discovery and Development Approach

We carefully evaluate and select our targets based on three key pillars, which provide a framework for optimizing our drug discovery and development efforts.

- Identify target mechanisms with a compelling biological rationale
  - *Current target mechanisms of focus include transcriptional regulation, deoxyribonucleic acid, or DNA, repair pathway, cell cycle regulation, exploitation of synthetic lethality and brain penetrant molecules.*
- Leverage our advanced medicinal chemistry capabilities to create better product candidates
  - *We view all target classes equally and strive to invent clinical candidates that meet our desired target product profiles. Clinical candidates from all programs to-date have been internally designed and developed.*
- Pursue targets that drive cancers with high unmet need
  - *Focus on targets that allow us to select patients and cancers with high unmet need with no approved therapies, or patient populations that are underserved by approved treatments.*

Once we have identified optimal targets using the three pillars above, we engage our unique discovery engine to invent and develop molecules rapidly and efficiently. We believe our expertise, capabilities and experience to select high value biological targets and invent molecules with an optimized balance of biological and chemical properties differentiates us from others in the precision oncology space. We believe our unique discovery engine will enable us to file a new IND every 12 to 18 months.

We design our clinical trials to leverage the broad utility of our compounds with a focus on efficient regulatory pathways to enable our potentially transformative medicines to potentially quickly reach patients with high unmet medical need. By focusing on validated cancer signaling pathways and early clinical proof-of-concept, we seek to advance our programs through expedited approval processes, as available. We believe that we can generate proof-of-concept clinical data to guide our future regulatory pathways to approval.

## Our Strategy

We aim to create better targeted and more effective cancer therapies. Our goal is to transform the lives of patients with cancer by leveraging the core competencies of our experienced team in medicinal chemistry, cancer biology and clinical development to bring novel drugs to market. We intend to become a fully integrated oncology company on the foundation of drug discovery excellence to deliver novel precision oncology medicines to patients with underserved cancers by pursuing the following objectives:

- Leverage our cancer biology and medicinal chemistry expertise to strive to deliver one new IND every 12 to 18 months.
- Discover and develop differentiated small molecules NCEs in validated targets and first-in-class targets that address unmet needs of oncology patients.
- Rapidly progress our product candidates through clinical development in patients with solid tumors and hematological malignancies.
- Focus clinical development on underserved cancers and design clinical trials that allow for efficient decision-making with the highest probability of success and potential for rapid regulatory approval.
- Advance our product candidate pipeline in combination with internally discovered and third-party developed compounds.
- Evaluate strategic opportunities to accelerate development timelines and maximize the value of our product candidates.

## Cancer Background and Treatment

Cancer is the second-leading cause of death in the United States. Cancer is a disease of the genome caused by changes in DNA that alter cell behavior, growth, and division. These changes can cause cells to produce abnormal amounts of certain

proteins and/or to make aberrant proteins that do not function properly. It is widely understood that cancer cells can eventually evade therapies through mutations or other resistance mechanisms, limiting the long-term success of drug therapies.

Historically, cancer has been treated with surgery, radiation and drug therapy, with patients often receiving a combination of these treatment modalities. While surgery and radiation can be effective in patients with localized disease, drug therapies are often required when the cancer has spread beyond the primary site or is not amenable to resection.

Drug therapy is intended to kill or damage malignant cells by interfering with the biological processes that control development, growth, and survival of cancer cells. This treatment modality has evolved over time from the use of non-specific cytotoxic therapies to precision oncology medicines targeting molecular pathways or oncogenic drivers. These precision medicines are broadly known as targeted therapies.

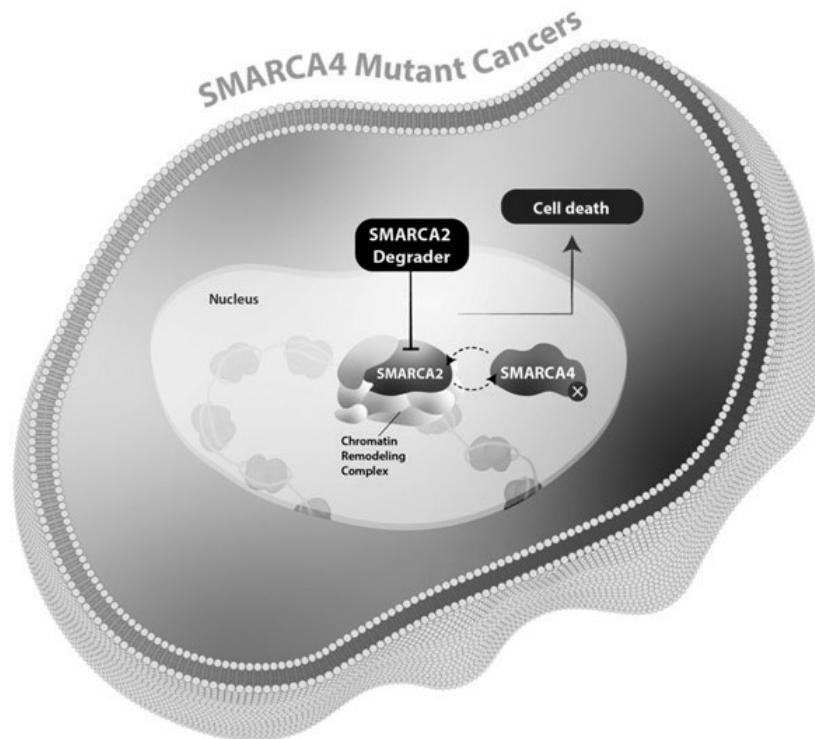
## Our Product Candidates

### SMARCA2 (BRM) targeted degrader program

#### *Background*

SMARCA2, or BRM, and its related family member, SMARCA4, or BRG1, are the enzymatic subunits of the SWI/SNF complex that regulates gene expression by allowing the DNA to be accessible for transcription to mature RNA, a process known as chromatin remodeling. *SMARCA4* is mutated in multiple cancers, including 10-12% of NSCLC, resulting in loss of SMARCA4 protein. Because the activity of either SMARCA2 or SMARCA4 is required for chromatin remodeling to occur, the *SMARCA4*-deficient cancer cells become highly dependent on SMARCA2 for their survival. Therefore, we believe targeting SMARCA2 in *SMARCA4*-deficient cancers will produce a strong synthetic lethality, resulting in *SMARCA4* mutant tumor cell death while sparing normal cells that express SMARCA4 protein.

Loss of SMARCA4 (BRG1) through mutation leads to dependency on SMARCA2 (BRM)





### ***Our SMARCA2 Degradation Program***

Due to the high homology between SMARCA2 and SMARCA4, there are few structural differences in the binding sites between the two proteins and thus selective SMARCA2 degradation has been a challenge for medicinal chemistry. Targeted protein degradation is a relatively new approach to degrade oncogenic proteins and has been shown to provide selective degradation of highly homologous proteins. A molecule capable of targeting a protein for degradation (degrader) typically contains a binding element to a targeted protein of interest (SMARCA2), a chemical linker and an E3 ligase binding element which allows for the formation of a ternary complex between the target, the degrader and the E3 ligase that induces ubiquitination and subsequent degradation of the targeted protein. Selectivity can be achieved, not only by the selective binding to the target (SMARCA2), but also through the optimization of the unique ternary complexes formed by the target (SMARCA2) versus its homologous protein (SMARCA4).

We used structure-based drug design to identify a novel series of potent and SMARCA2 binders and linked these binding elements to an E3 ligase binding domain to identify SMARCA2 degraders. Extensive structure activity relationships generated by the iterative synthesis and testing of >1000 compounds as of the date of this Annual Report on Form 10-K has allowed for the identification of specific structural motifs that provide >1000-fold selectivity for SMARCA2 degradation over SMARCA4 while maintaining potent SMARCA2 degradation, with DC50 < 10 nM. DC50 is a quantitative measure of how much of a compound is needed to achieve degradation of the target protein (SMARCA2) by 50%. We have designed our SMARCA2 degraders to be potent and selective to specifically inhibit SMARCA4-deficient human NSCLC cell lines and primary patient derived samples in vitro and in vivo at well tolerated doses. We completed IND-enabling studies and received IND clearance in October 2022 for PRT3789, a first-in-class, highly selective degrader of SMARCA2 protein, which along with SMARCA4 controls gene regulation through chromatin remodeling. PRT3789 is efficacious and well tolerated in preclinical models of SMARCA4 deleted/mutated cancers as monotherapy and in combination with standards of care. Patients with SMARCA4 mutations or deletions may have poor clinical outcomes and limited treatment options. Therefore, mutated or deleted SMARCA4 cancers provide a potential biomarker to select those patients most likely to respond to treatment with a highly selective SMARCA2 degrader.

PRT3789 is currently in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. To date PRT3789 has completed the fifth dose escalation cohort and demonstrated selective, potent and dose dependent degradation of SMARCA2 with an acceptable safety profile. Based on PK/PD and safety data to date, the Company expects to conclude monotherapy dose escalation in the middle of 2024 and identify recommended phase 2 doses. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations has been initiated. Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in combination with docetaxel, evaluate efficacy, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into a registrational clinical trial.

Our discovery team has identified a series of highly selective and orally bioavailable SMARCA2 degraders. The lead oral molecule, PRT7732, is currently in IND enabling studies and on track to enter Phase 1 clinical development in the second half of 2024. PRT7732 is structurally distinct from PRT3789 and in addition, may provide clinically meaningful differences, more patient-friendly dosing and may have utility in earlier lines of therapy.

### **CDK9 Program**

#### ***Overview***

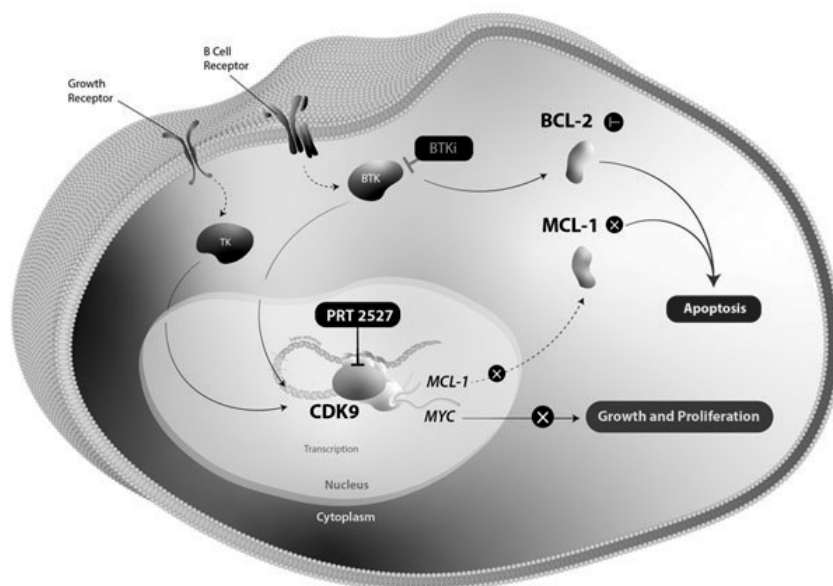
CDK9 has emerged as an essential regulator of cancer-promoting transcriptional programs, including those driven by *MCL1*, *MYC* and *MYB*. Inhibition of CDK9 is therefore an attractive therapeutic approach to target specifically genomically selected cancers. We have applied our internal expertise to design PRT2527 as a potent inhibitor of CDK9 that exhibits high kinome selectivity, PK properties and solubility that we believe may broaden the therapeutic window of CDK9 inhibition. A Phase 1 trial is underway evaluating escalating IV doses of PRT2527 as a monotherapy in patients with selected solid tumors, including sarcoma, prostate cancer, lung cancer, and other cancers with genomic alterations that lead to MYC dependence.

#### ***Background***

Cyclin dependent kinases, or CDKs, are a family of closely related serine/threonine kinases that have demonstrated activity in multiple cancers. The first inhibitors of two of the family members, CDK4 and CDK6, gained FDA approval for HR+ metastatic breast cancer in 2015 and are now broadly used. In contrast to CDK4 and CDK6, which regulate cell cycle progression and proliferation, it is now understood that other members of the CDK family play important roles in regulating

transcription. CDK9 specifically phosphorylates RNA polymerase II to generate mature mRNA. Given its fundamental role in transcription, CDK9 has emerged as a central node in the transcriptional addiction of cancer.

### CDK9 regulates expression of several oncogenes that drive cancer cell growth and resistance



Importantly, inhibition of CDK9 in cancer has been shown to preferentially deplete short-lived transcripts including key anti-apoptotic genes such as MCL1 and oncogenic transcription factors such as MYC and MYB. Preclinical evidence demonstrates that CDK9 inhibition represses MCL1 and thereby overcomes resistance to the BCL2 inhibitor venetoclax. Additionally, preclinical studies suggest that CDK9 inhibition perturbs MYC-mediated signaling and produces synthetic lethality in nuclear protein of the testis midline carcinoma, hepatocellular carcinoma and additional solid tumors. Our patient selection strategy in clinical trials will strive to exploit these relationships by identifying cancers with molecular evidence of *MCL1* and/or *MYC* dysregulation.

#### ***Our CDK9 Inhibitor: PRT2527***

Although various non-selective CDK9 inhibitors have progressed through clinical development, they have been significantly limited by narrow therapeutic windows due to adverse effects, including bone marrow suppression, nausea and GI effects. We have utilized structure-based design to identify a novel, structurally differentiated series of CDK9 inhibitors. Iterative synthesis and testing of over 600 compounds allowed for the identification of PRT2527, which has improved potency and kinase selectivity compared to AZ4573, the most advanced CDK9-selective inhibitor currently in development. The PK and physical properties of PRT2527 are suitable for IV or subcutaneous dosing.

In preclinical models, PRT2527 reduced MCL1 and MYC protein levels and was highly active in the *MYC*-amplified MV4-11 xenograft model at well-tolerated doses. Upon evaluation of additional models, PRT2527 treatment demonstrated robust efficacy in both hematological malignancies and solid tumor models with *MYC* dysregulation. Our preclinical studies suggest that PRT2527 demonstrates high kinase selectivity and potency, providing opportunity for a wider therapeutic index compared to less selective CDK9 inhibitors, allowing for rapid development in combinations.

In February 2023, we signed an agreement with BeiGene for them to supply zanubrutinib, a BTK inhibitor, for further study in combination with PRT2527. PRT2527 has completed a Phase 1 multi-dose escalation study (NCT05159518) in patients with solid tumors. In this study, PRT2527 was shown to achieve high levels of target inhibition and the potential to be better tolerated than existing CDK9 inhibitors, specifically, managing neutropenia and an absence of meaningful gastrointestinal events or hepatotoxicity. The observed dose-dependent downregulation of MYC and MCL1 mRNA expression, CDK9 transcriptional targets, was consistent with the degree of target engagement required for preclinical efficacy. As predicted by the preclinical models, 12 mg/m<sup>2</sup> QW dosing showed optimal target inhibition and has been

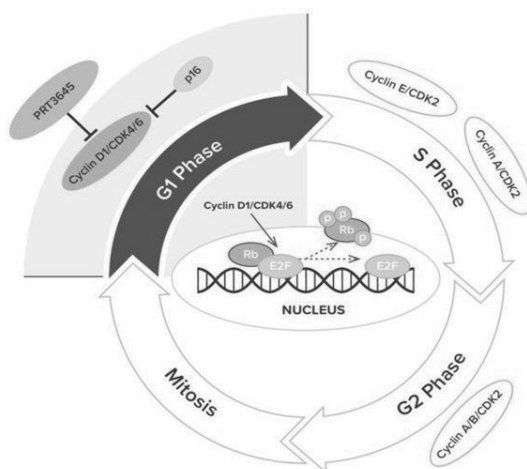
selected as the optimal dose. The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530). In this study, PRT2527 is advancing in monotherapy hematological indications, such as B-cell malignancies and AML, and has initiated the combination with zanubrutinib in B-cell malignancies. We expect to complete the monotherapy dose escalation in B-cell malignancies in the middle of 2024. A second cohort of patients with AML is expected to initiate in the first half of 2024.

## CDK4/6 Program

### Background

Among the CDK subfamily of kinases, CDK4 and CDK6 are the master regulators that control entry of cells into cell cycle. Given the central roles that CDK4 and CDK6 play in cell cycle regulation, dysregulation of the CDK4/CDK6 pathway has been frequently observed in cancer and CDK4/CDK6 have been intensively investigated as potential therapeutic targets for cancer treatment. The approval of three CDK4/CDK6 selective inhibitors in combination with endocrine therapies, to treat hormone receptor, or HR, positive and human epidermal growth factor receptor 2, or HER2, negative metastatic breast cancer, has further validated this hypothesis.

Next generation CDK 4/6 inhibitor with improved tolerability and tissue penetrance could translate into activity in areas of unmet need beyond HR+ breast cancer.



In addition to the role of CDK4/6 in ER+ metastatic breast cancer, large scale genomic studies revealed that the CDK4/CDK6 pathway is disrupted in the majority of gliomas, suggesting CDK4/CDK6 may be good targets for glioblastoma, or GBM. Genomic studies also identified the CDK4/6 pathway as one of three most altered and actionable genetic alternations in brain metastasis. However, despite positive preclinical data supporting targeting CDK4/CDK6 to treat CNS cancers, clinical development of CDK4/CDK6 inhibitors for GBM or brain metastases has not been successful, likely due to the inability of current inhibitors to penetrate the blood-brain barrier (BBB) and achieve effective concentrations in the brain. Recent studies have also demonstrated that CDK4/6 pathway activation can serve as a resistance mechanism to other targeted therapies, including inhibitors of the RAS and HER2 pathways, suggesting a combination potential in other tumor types with unmet need. Together, these data suggest that a next generation CDK4/6 inhibitor with improved tissue penetration and combinability could extend the therapeutic potential of this target class.

### Our CDK4/6 Inhibitor: PRT3645

Structure based design, iterative compound synthesis and testing led to the identification of PRT3645, a highly brain and tissue penetrant molecule that potently targets CDK4/6 with biased selectivity for CDK4. In cellular assays, PRT3645 inhibits phosphorylation of RB, a substrate of CDK4/CDK6, with low nanomolar activity. Consistent with this, PRT3645 treatment results in concentration-dependent inhibition of cell proliferation in glioblastoma (GBM) cell lines, ER+/HER2- and HER2+ breast cancer lines and NSCLC cell lines. In vivo, orally administered PRT3645 was well tolerated and highly efficacious in a dose-dependent manner in orthotopic human breast cancer brain metastasis and GBM models. In addition, combined activity was observed when PRT3645 was dosed with inhibitors of the RAS pathway in NSCLC or CRC models or in combination with HER2 pathway inhibitors in HER2+ breast cancer models, suggesting a combination potential in other tumor types with unmet need. In a head-to-head comparison, PRT3645 demonstrated a tissue: plasma ratio that was >10x

higher than approved CDK4/6 inhibitors. In July 2022, we received IND clearance for PRT3645. A Phase 1 multi-dose escalation clinical trial of PRT3645 is underway and we intend to reach a biologically active dose confirmation. At the 2023 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, we presented data, showing that treatment with PRT3645 was associated with a substantial decrease in pRb and Ki67 expression, indicating a high level of target engagement at the doses evaluated. Also, PRT3645 was generally well tolerated in the initial three dose cohorts of patients with no clinically meaningful gastrointestinal, hematologic or neurological events reported to date, leveraging its enhanced selectivity profile. We intend to complete the dose escalation portion of the Phase 1 clinical trial of PRT3645 this year and following its completion to explore continued clinical development with external partners.

### **MCL1 Inhibitor: PRT1419**

PRT1419 is designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. PRT1419 has been optimized to provide maximal coverage of the target while maintaining an adequate tolerability window. Based on our preclinical data, as well as published third-party data, we believe that hematological malignancies are particularly sensitive to MCL1 inhibitors. MCL1 upregulation has been noted as a mechanism of acquired resistance to venetoclax and Tyrosine Kinase Inhibitors, or TKIs. We concluded a Phase 1 development of PRT1419 and established a confirmation dose in hematological cancers. Based on the potential to address the intended patient population with the CDK9 inhibitor which potently inhibits MCL-1, we decided to prioritize our CDK9 inhibitor, PRT2527, over PRT1419.

### **Intellectual Property**

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the compositions of matter of our product candidates, their methods of use, related technology, and other inventions that are important to our business.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, and know-how related to our business, to defend and enforce our patents, to preserve the confidentiality of our trade secrets, and to operate without infringing valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of precision oncology.

As more fully described below, our patent portfolio includes, inter alia, patent families with claims directed to compositions of matter for, and methods of using, compounds that degrade SMARCA2 and PRT2527, PRT3645, and other compounds. The patent portfolio currently comprises of 309 patents and patent applications:

(A)(i) 12 issued U.S. patents, (ii) 29 U.S. non-provisional patent applications, and (iii) 40 U.S. provisional patent applications; and

(B)(iv) 15 PCT patent applications, (v) 60 issued foreign patents including patents in European jurisdictions, and (vi) 153 foreign patent applications.

As of the present filing, a total of twelve U.S. patents have been issued, which are wholly owned by us. Specifically, one U.S. patent directed to PRT1419 has issued and is expected to expire no earlier than November 8, 2039, one U.S. patent directed to PRT2527 has issued and is expected to expire no earlier than September 2040, one U.S. patent directed to PRT3645 has issued and is expected to expire no earlier than September 2041, and one patent has issued for compounds that degrade SMARCA2, which is expected to expire no earlier than June 2041.

In addition to our filings in the U.S., we own patent applications that are pending in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. Included in these applications are claims directed to the PRT1419, PRT2527, and SMARCA compositions and methods of using the same therapeutically. For the PRT1419 compound, the patents from these applications, if issued, are expected to expire no earlier than November 2039, subject to any disclaimers or extensions. For the PRT2527 compound, the patents from these applications, if issued, are expected to expire no earlier than September 2040, subject to any disclaimers or extensions. For the SMARCA compounds, the one issued patent and patents from other applications, if issued, are expected to expire no earlier than June 2041, subject to any disclaimers or extensions. For the PRT3645 compound, the patents from these applications, if issued, are expected to expire in September 2041, subject to any disclaimers or extensions available under the Hatch-Waxman Act.

The patent portfolios for our programs are summarized below.

#### ***PRT3789 and Other SMARCA2 Degraders***

Our PRT3789 and Other SMARCA2 Degraders patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims among other things, SMARCA degraders and other compounds, pharmaceutical compositions comprising SMARCA degraders, and methods of using such compounds. The portfolio further includes seven pending U.S. non-provisional applications, which claim, among other things, genera of compounds that encompass SMARCA2 and/or related degraders, pharmaceutical compositions comprising those degraders, and methods of treating cancer with those degraders.

A related PCT application corresponding to the issued U.S. patent was filed and corresponding national phase applications were filed in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. A related PCT application corresponding to the U.S. non-provisional application was also filed on the same day as well as corresponding national phase applications in Australia, Brazil, Canada, China, Eurasia, Europe, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. One PCT application pertaining to combination therapy including the SMARCA2 degraders was also filed.

The SMARCA2 Degraders patent portfolio also includes twelve pending U.S. provisional applications that, among other things, encompass SMARCA2 and/or related inhibitors, pharmaceutical compositions comprising those inhibitors, and methods of treating cancer with those inhibitors. Any patents granted that claim priority to this provisional application could expire as early as 2044, subject to any disclaimers or extensions available under the Hatch-Waxman Act.

#### ***PRT3645 and Other CDK Inhibitors***

Our PRT3645 patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims among other things, PRT3645 and other compounds, pharmaceutical compositions comprising PRT3645, and methods of using such compounds. The portfolio further includes one pending U.S. non-provisional patent application, which claims among other things, PRT3645 related compounds, pharmaceutical compositions comprising PRT3645 related compounds, and methods of using such compounds.

A related PCT application corresponding to the issued U.S. patent, *supra*, was filed in 2021, and corresponding national phase applications were filed in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. A PCT application that claims among other things, PRT3645 polymorphic compounds and methods of using such compounds, was filed in 2022.

The PRT3645 patent portfolio also includes five pending U.S. provisional applications that relate to among other things, methods of inhibiting CDK using PRT3645 related compounds and methods of treating certain cancers. Any patents granted that claim priority to these provisional applications could expire as early as 2044, subject to any disclaimers or extensions available under the Hatch-Waxman Act.

Our Other CDK Inhibitors portfolio is wholly owned by us. The portfolio includes six pending U.S. non-provisional patent applications, which claims among other things, CDK inhibitor compounds, pharmaceutical compositions comprising CDK related compounds, and methods of using such compounds.

A related PCT application corresponding to the U.S. non-provisional was filed on December 17, 2021, and corresponding national phase applications were filed in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. Four other related PCT applications were filed in 2023.

The CDK Inhibitors patent portfolio also includes one pending U.S. provisional application that relate to among other things, methods of inhibiting CDK using compounds and methods of treating certain cancers. Any patents granted that claim priority to this provisional application could expire as early as 2044, subject to any disclaimers or extensions available under the Hatch-Waxman Act.

#### ***PRT2527***

Our PRT2527 patent portfolio is wholly owned by us. The portfolio includes one issued U.S. patent, which claims among other things, PRT2527 and other compounds, pharmaceutical compositions comprising PRT2527, and methods of using such compounds. The portfolio further includes three pending U.S. non-provisional applications: (i) a U.S. continuation application, which claims among other things, PRT2527 related compounds, pharmaceutical compositions comprising PRT2527 related compounds, and methods of using such compounds, which was effectively filed in 2020; (ii) a U.S. application, which claims among other things, PRT2527 related compounds, pharmaceutical compositions comprising

PRT2527 related compounds, and methods of using such compounds, which was filed in 2023; and (iii) a U.S. application, directed to additional uses of PRT2527 and related compounds, which was filed in 2022.

A related PCT application corresponding to the issued U.S. patent was filed in 2020, and corresponding national phase applications were filed in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, South Africa, South Korea, and Ukraine. A related PCT application corresponding to the U.S. non-provisional application in (iii), *supra*, was filed in 2022. Another PCT application that claims among other things, PRT2527 crystalline forms and salts and methods of using such compounds, was filed in 2022.

The PRT2527 patent portfolio also includes six pending U.S. provisional applications that relate to among other things, methods of inhibiting CDK9 using PRT2527 related compounds and methods of treating certain cancers. Any patents granted that claim priority to these provisional applications could expire as early as 2044, subject to any disclaimers or extensions available under the Hatch-Waxman Act.

### ***Other***

In addition, we have patent portfolios that are directed to a number of different compounds other than PRT1419, PRT2527, PRT3645, SMARCA2 Degraders, and CDK inhibitors. We have patent applications directed to compounds that target resistance mechanisms in cancer. We expect to maintain some of these applications in the United States and to also file in foreign countries.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In the countries in which we file, the patent term is 20 years from the earliest non-provisional filing date, subject to any disclaimers or extensions. The term of a patent in the United States can be adjusted due to any failure of the United States Patent and Trademark Office following certain statutory and regulation deadlines for issuing a patent.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for a portion of the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the original expiration of the patent. The protection provided by a patent varies from country to country, and is dependent on the type of patent granted, the scope of the patent claims, and the legal remedies available in a given country.

Obtaining patent protection is not the only method that we employ to protect our proprietary rights. We also utilize other forms of intellectual property protection, including trademark, copyright, and trade secrets, when those other forms are better suited to protect a particular aspect of our intellectual property. Our belief is that our proprietary rights are strengthened by our comprehensive approach to intellectual property protection. 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 during the course of the individual'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.

### **Manufacturing**

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely for the foreseeable future, on third parties for the manufacture of our product candidates for preclinical and clinical testing, including pharmaceutical ingredients and clinical drug supply, as well as for commercial manufacture of any drugs that we may commercialize. We obtain our supplies from these manufacturers on a purchase order basis and do not have long-term supply arrangements in place. We do not own in-house warehouse facilities. We rely on third parties for storage and distribution of drug substance and drug product. We do not currently have arrangements in place for redundant supply for active pharmaceutical ingredients and drug product. As our development programs progress and we build new process efficiencies, we expect to continually evaluate this strategy with the objective of satisfying demand for registration trials and, if approved, the manufacture, sale and distribution of commercial products.

### **Commercialization**

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. If we are successful in obtaining the necessary regulatory approval, we may pursue commercialization on our own or seek to collaborate with a third party for commercialization, particularly outside the United States.

The biotechnology and pharmaceutical industries are characterized by the rapid evolution of technologies and understanding of disease etiology, intense competition and a strong emphasis on intellectual property. We believe that our approach, strategy, scientific capabilities, know-how and experience provide us with competitive advantages. However, we expect substantial competition from multiple sources, including major pharmaceutical, specialty pharmaceutical, and existing or emerging biotechnology companies, academic research institutions and governmental agencies and public and private research institutions worldwide. Many of our competitors, either alone or through collaborations, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient enrollment in clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. As a result, our competitors may discover, develop, license or commercialize products before or more successfully than we do.

## Competition

We face competition from segments of the pharmaceutical, biotechnology and other related markets that pursue the development of precision oncology therapies optimized to target the key driver mechanisms in cancers with high unmet need. Several biopharmaceutical companies, including Arvinas Inc., Aurigene, Black Diamond Therapeutics, Inc., Boehringer Ingelheim, C4 Therapeutics, Constellation Pharmaceuticals, Inc., Eli Lilly and Company, F. Hoffman-La Roche, Foghorn Therapeutics Inc., Fochon Pharmaceuticals, G1 Therapeutics Inc., Genentech, Kronos Bio, Inc., Kura Oncology, Inc., Kymera Therapeutics Inc., Mirati Therapeutics Inc., Nuvation Bio Inc. Repare Therapeutics Inc., Revolution Medicines, Inc., Relay Therapeutics, Inc., Springworks Therapeutics, Inc., Syndax Pharmaceuticals, Inc., and Zentalis Pharmaceuticals, Inc., are developing precision oncology medicines. In addition, we may face competition from companies developing product candidates that are based on targeting pathways of adaptive resistance, including Amgen Inc., AbbVie Inc., AstraZeneca plc, GlaxoSmithKline plc, Ideaya Biosciences, Johnson & Johnson Services, Inc., Pfizer Inc., Tango Therapeutics, Inc., Vincerx Pharma, Inc., Novartis AG, and Gilead Sciences, Inc.

Furthermore, we also face competition more broadly across the oncology market for cost-effective and reimbursable cancer treatments. 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 methods. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates, if any are approved, may compete with these existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates may not be competitive with them. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. As a result, obtaining market acceptance of, and gaining significant share of the market for, any of our product candidates that we successfully introduce to the market may pose challenges. In addition, many companies are developing new oncology therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

For our CDK9 program, PRT2527, AstraZeneca (AZD4573), Vincerx (VIP512), and Kronos (KB-0742) have CDK9 programs in Phase 1 clinical trials. For our CDK4/6 inhibitor program, PRT3645, Novartis (ribociclib), Lilly (abemaciclib), Pfizer (53albociclib), G1 Therapeutics (G1T38), and Fochon Pharmaceuticals (FCN-437) have clinical trials ongoing. For our SMARCA 2 (BRM) degrader program, other companies, including Amgen, Aurigene, C4 Therapeutics, F. Hoffman-La Roche, Foghorn Therapeutics, Inc., Kymera Therapeutics, Arvinas, Genentech, Boehringer Ingelheim, and Lilly have publicly disclosed their pre-clinical research efforts.

We could see a reduction or elimination in our commercial opportunity if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient to administer, are less expensive or with more favorable labeling than our product candidates. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

## **Government Regulation**

Government authorities in the U.S., at the federal, state and local level, and in other countries and jurisdictions extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products such as those we are developing. 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.

### ***FDA Approval Process***

In the U.S., pharmaceutical products are subject to extensive regulation by the FDA, the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and other federal and state statutes and regulations govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending new drug applications, or NDAs, warning or untitled letters, product recalls, product seizures, import detention, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution. We may also be debarred or excluded from participation in government healthcare programs. Regulatory requirements governing our business are evolving. FDA also continually issues guidance documents that provide FDA's interpretation of its laws and regulations, as well as FDA's approach to scientific issues and questions.

Pharmaceutical product development for a new product or certain changes to an approved product in the U.S. typically involves preclinical laboratory and animal tests, the submission to FDA of an IND which must become effective before clinical testing in the U.S. may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including Good Laboratory Practice, or GLP, regulations and other applicable laws or regulations. The results of preclinical testing are submitted to FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, a proposed clinical trial protocol, and any available clinical data or literature on the product candidate. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If FDA has not placed the study on clinical hold within this 30-day period, the clinical trial proposed in the IND may begin.

Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with Good Clinical Practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to FDA as part of the IND. Sponsors will also be required to provide FDA with diversity action plans.

FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. Imposition of a clinical hold may be full or partial. The study protocol and informed consent information for patients in clinical trials must also be submitted for approval to an institutional review board, or IRB, and ethics committee for approval. An IRB considers among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits, and whether the planned human subject protections are adequate. The IRB will also monitor the clinical trial until completed. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. Progress reports detailing the results of the clinical trials must be submitted at least annually to FDA and the IRB and more frequently if serious adverse events or other significant safety information is found. Additionally,



some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated checkpoints based on access to certain data from the trial.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap, be divided, or be combined. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, mechanism of action, absorption, metabolism distribution, excretion, side effects associated with increasing doses, and, if possible, early evidence of effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a drug demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single Phase 3 trial may be sufficient in rare instances, including (1) where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible or (2) when in conjunction with other confirmatory evidence. In some instances, FDA may condition approval of an NDA on the applicant's agreement to conduct additional clinical trials to further assess the product's safety and effectiveness after approval, to answer unresolved questions, or to ensure that population representative data is collected. Such post-approval trials are typically referred to as Phase 4 studies. The results of Phase 4 studies can confirm or refute the effectiveness of a product candidate, and can provide important safety information.

These Phases may overlap or be combined. For example, a Phase 1/2 clinical trial may contain both a dose-escalation stage and a dose-expansion stage, the latter of which may confirm tolerability at the recommended dose for expansion in future clinical trials (as in traditional Phase 1 clinical trials) and provide insight into the anti-tumor effects of the investigational therapy in selected subpopulation(s).

Concurrent with clinical trials, companies usually complete additional nonclinical studies and must also develop additional information about the physical characteristics of the product candidate and finalize a manufacturing process for the product candidate in commercial quantities in accordance with current Good Manufacturing Practice, or cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate. Further, appropriate packaging must be selected and tested and adequate stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Typically, during the development of oncology therapies, all subjects enrolled in Phase 1 clinical trials are disease-affected patients and, as a result, considerably more information on clinical activity may be collected during such trials than during Phase 1 clinical trials for non-oncology therapies.

A single pivotal trial may be sufficient in rare instances to provide substantial evidence of effectiveness (generally subject to the requirement of additional post-approval studies).

The manufacturer of an investigational drug in a Phase 2 or 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access.

After completion of the required clinical testing, an NDA is prepared and submitted to FDA. FDA approval of the NDA is required before marketing of the product may begin in the U.S. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business, provided that certain very specific qualifying criteria are met. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication. The applicant under an approved NDA is also subject to annual program fees. The FDA adjusts the user fees on an annual basis, and the fees typically increase annually.

FDA reviews each submitted NDA before it determines whether to file it, based on the agency's threshold determination that it is sufficiently complete to permit substantive review, and FDA may request additional information. The FDA must make a decision on whether to file an NDA within 60 days of receipt, and such decision could include a refusal to file by the FDA. Once the submission is filed, FDA begins an in-depth review of the NDA. FDA has agreed to certain performance goals in the review of NDAs. FDA has set a performance goal for reviewing standard applications as within ten months of acceptance of an NDA for filing; and for priority review drugs, within six months of acceptance of an NDA for filing. Drugs may qualify for priority review if they would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition when compared to standard applications. The review process for both standard and priority review may be extended by FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission. The FDA does not always meet its goal dates for standard and priority NDAs, and the review process can be extended by FDA requests for additional information or clarification.

FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an outside advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, FDA will conduct a pre-approval inspection or remote regulatory assessment of the manufacturing facilities for the new product to determine whether they comply with cGMP requirements. FDA will not approve the product 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. The FDA will not approve the product unless cGMP compliance is satisfactory. The FDA also typically inspects or conduct a remote regulatory assessment of one or more clinical trial sites to ensure compliance with GCP requirements and the integrity of the data supporting safety and efficacy.

After FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter, or CRL, generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for FDA to reconsider the application, such as additional clinical data, additional pivotal 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 applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, engage in formal dispute resolution or request an opportunity for a hearing. FDA has committed to reviewing 90% of resubmissions in two or six months depending on the type of information included. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval.

If, or when, the deficiencies identified in the CRL have been addressed to FDA's satisfaction in a resubmission of the NDA, FDA will issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks to patients. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

There is no guarantee that FDA will approve an NDA. Moreover, even if marketing authorization of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed, the product may have labeling that includes significant restrictions, warnings, including black box warnings, and contraindications, the regulatory authorities may not approve label claims necessary for successful product marketing, or the approval may be subject to significant conditions of approval, including the requirement of a REMS.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of an NDA supplement or, in some instances, a new NDA, before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

### ***Disclosure of Clinical Trial Information***

Sponsors of clinical trials of FDA regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial, provided that certain criteria are met and certifications are provided. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

### ***Expedited Development and Review Programs***

#### ***Fast Track Designation***

Fast track designation may be granted for a product that is intended to treat a serious or life-threatening disease or condition for which preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. The sponsor of an investigational drug product may request that FDA designate the product candidate for a specific indication as a fast-track drug concurrent with, or after, the submission of the IND for the product candidate. FDA must determine if the product candidate qualifies for fast-track designation within 60 days of receipt of the sponsor's request. For fast track products, sponsors may have greater interactions with the FDA and the FDA may potentially initiate review of sections of a fast track product's NDA before the application is complete, referred to as "rolling review." The sponsor must provide, and the FDA must approve, a schedule for the submission of the application and the sponsor must pay applicable user fees. At the time of NDA filing, the FDA will determine whether to grant priority review designation. FDA will grant such designation if the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Additionally, fast track designation may be withdrawn if FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

#### ***Accelerated Approval***

Accelerated approval may be granted for a product that is intended to treat a serious or life-threatening condition and that generally provides a meaningful therapeutic advantage to patients over existing treatments. A product eligible for accelerated approval may be approved on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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. 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 studies to demonstrate a clinical or survival benefit. The accelerated approval pathway is contingent on a sponsor's agreement to conduct additional post-approval confirmatory studies to verify and describe the product's clinical benefit. These confirmatory trials must be completed with due diligence. By the date of approval of an accelerated approval product, FDA must specify the conditions for the required post approval studies, including enrollment targets, the study protocol, milestones, and target completion dates. FDA may also require that the confirmatory Phase 4 studies be commenced prior to FDA granting a product accelerated approval. Reports on the progress of the required Phase 4 confirmatory studies must be submitted to FDA every 180 days after approval. If the trials fail to verify the clinical benefit of the drug or biologics product, the FDA may withdraw approval of the application through a statutorily defined streamlined process. Failure to conduct the required Phase 4 confirmatory studies or to conduct such studies with due diligence, as well as failure to submit the required update reports can subject a sponsor to penalties. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

#### ***Breakthrough Therapy Designation***

FDA is also required to expedite the development and review of applications for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new product candidate may request that FDA designate the product candidate

for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the product candidate. FDA must determine if the product candidate qualifies for a Breakthrough Therapy Designation within 60 days of receipt of the sponsor's request. The FDA may take certain actions with respect to breakthrough therapies, including but not limited to 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, granting priority review status or Fast Track Designation, reviewing applications on a rolling basis, and taking other steps to design the clinical studies in an efficient manner.

### ***Orphan Drugs***

Under the Orphan Drug Act, FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States but for which there is no reasonable expectation that the cost of developing and making the product for this type of disease or condition will be recovered from sales of the product in the United States. Additionally, sponsors must present a plausible hypothesis for clinical superiority to obtain orphan designation if there is a product already approved by the FDA that is considered by the FDA to be the same as the already approved product and is intended for the same indication. This hypothesis must be demonstrated to obtain orphan exclusivity.

Orphan drug designation must be requested before submitting an NDA. After FDA grants orphan drug designation, the identity of the drug and its potential orphan use are disclosed publicly by FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

FDA's regulations provide flexibility in meeting approval standards for new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists, such that FDA may exercise scientific judgment in determining the kind and quantity of data required for approval and during development programs. Per guidance issued by FDA in 2023 with respect to rare diseases, "[t]his flexibility extends from the early stages of development to the design of adequate and well-controlled clinical investigations required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use." FDA states that it "is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease...."

The first NDA applicant to receive FDA approval for a particular active moiety to treat a rare disease for which it has such designation is entitled to a seven-year exclusive marketing period in the U.S. for that product, for that indication. During the seven-year exclusivity period, FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care, or in instances of drug supply issues. Orphan drug exclusivity does not prevent FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Other benefits of orphan drug designation include tax credits for certain research and an exemption from the NDA user fee.

It bears noting that the exact scope of orphan drug exclusivity may be an evolving space. A 2021 judicial decision, *Catalyst Pharms., Inc. v. Becerra*, challenged and reversed an FDA decision on the scope of orphan product exclusivity for the drug, Firdapse. Under this decision, orphan drug exclusivity for Firdapse blocked approval of another company's application for the same drug for the entire disease or condition for which orphan drug designation was granted, not just the disease or condition for which approval was received. In a January 2023 Federal Register notice, however, the FDA stated that it intends to continue to apply its regulations tying the scope of orphan-drug exclusivity to the uses or indications for which a drug is approved. The exact scope of orphan drug exclusivity will likely be an evolving area.

### ***Pediatric Information***

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. However, compliance may be required if approval is sought for other indications for which the product has not received orphan designation.

Separately, product candidates intended for the treatment of adult cancer which are directed at molecular targets that the FDA determines to be substantially relevant to the growth or progression of pediatric cancer, must submit, with the marketing application, reports from molecularly targeted pediatric cancer investigations designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each applicable age group, to inform potential pediatric labeling. The FDA may, on its own initiative or at the request of the applicant, grant deferrals or waivers of some or all of this data, as above. Orphan products are not exempt from this requirement.

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity—patent or nonpatent—for a drug if certain conditions are met. Conditions for exclusivity include FDA’s determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

### ***Post-Approval Requirements***

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Drugs may be marketed only for the approved indications and in a manner consistent with the approved labeling. Promotion and advertising must also be truthful and non-misleading, must be adequately substantiated, and with a fair balance between product benefit claims and risks, among other requirements. In 2023, FDA issued a final rule and a guidance on risk and efficacy disclosures in direct-to-consumer advertising, and a guidance on communication of off-label scientific information about approved products. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with the laws and regulations governing advertising and promotion can have negative consequences, including FDA and other governmental authority enforcement actions.

Adverse event reporting and submission of periodic reports are required following FDA approval of an NDA. FDA also may require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control, drug manufacture, packaging and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with FDA and certain state agencies and list the drugs produced. The information that must be submitted to FDA regarding manufactured products was expanded through the Coronavirus Aid, Relief, and Economic Security, or CARES Act to include the volume of drugs produced during the prior year. Registration with FDA subjects entities to periodic unannounced inspections or remote regulatory assessments by FDA, during which the Agency inspects or assesses manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered. Sponsors are further subject to various requirements related to FDA drug shortage and manufacturing volume reporting, supply chain security, such as risk management plan requirements, and the promotion of supply chain redundancy. Legislation and executive actions have also been issued to encourage domestic manufacturing, as well as to decrease drug prices. For instance, FDA recently approved a plan that was submitted by Florida to import drugs from Canada.

Quality control and manufacturing procedures must continue to conform to cGMP after approval, including quality control and quality assurance and maintenance of records and documentation. Changes to the product manufacturing process often require prior FDA approval or notification before being implemented. FDA regulations also require the investigation and correction of any identified deviations from cGMP and specifications, and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers.

### ***The Hatch-Waxman Amendments***

#### ***Orange Book Listing***

Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch Waxman Amendments, NDA applicants are required to identify to FDA each patent whose claims cover the applicant’s drug or approved method of using the drug. Upon approval of a drug, the applicant must update its listing of patents to the NDA in timely fashion and each of the patents listed in the application for the drug is then published in the FDA’s Approved Drug

Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. In an effort to clarify which patents must be listed in the Orange Book, in January 2021, Congress passed the Orange Book Transparency Act of 2020, which largely codifies FDA's existing practices into the FD&C Act. Listing patents in the Orange Book that do not qualify for listing can be considered to be anticompetitive conduct and, in 2023, the Federal Trade Commission sent letters to a number of companies with respect to certain patents that agency asserted were improperly listed or inaccurate.

Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredient(s), strength, route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. An approved ANDA product is considered to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, pre-clinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved under the ANDA pathway are commonly referred to as "generic equivalents" to the listed drug and can often be substituted by pharmacists under prescriptions written for the original listed drug pursuant to each state's laws on drug substitution.

The ANDA applicant is required to certify to the FDA concerning any patents identified for the reference listed drug in the Orange Book. Specifically, the applicant must certify to each patent in one of the following ways: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. For patents listed that claim an approved method of use, under certain circumstances the ANDA applicant may also elect to submit a section viii statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents through a Paragraph IV certification, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA-holder and patentee(s) within certain specified timeframes (referred to as the "notice letter"). The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice letter. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months from the date the notice letter is received, expiration of the patent, the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed, or a decision in the patent case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired. In some instances, an ANDA applicant may receive approval prior to expiration of certain non-patent exclusivity if the applicant seeks, and FDA permits, the omission of such exclusivity-protected information from the ANDA prescribing information.

### *Exclusivity*

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by FDA in any other NDA, that drug receives five years of marketing exclusivity during which FDA cannot receive any ANDA seeking approval of a generic version of that drug unless the application contains a Paragraph IV certification, in which case the application may be submitted one year prior to expiration of the NCE exclusivity. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA for a generic version of the drug may be filed before the expiration of the exclusivity period.

Certain changes to an approved drug, such as the approval of a new indication, the approval of a new strength, and the approval of a new condition of use, are associated with a three-year period of exclusivity from the date of approval during which FDA cannot approve an ANDA for a generic drug that includes the change. To qualify for three-year exclusivity, there must be new clinical investigations, other than bioavailability studies, supporting the application, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application. In some instances, an ANDA applicant may receive approval prior to expiration of the three-year exclusivity if the applicant seeks, and FDA permits, the omission of such exclusivity-protected information from the ANDA package insert.

### *Patent Term Extension*

The Hatch Waxman Amendments permit a patent term extension as compensation for patent term lost during the FDA regulatory review process. Patent term extension, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. After NDA approval, owners of relevant drug patents may apply for the extension. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be reduced for any time FDA determines that the applicant did not pursue approval with due diligence.

The United States Patent and Trademark Office, or USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. However, the USPTO may not grant 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 requested.

The total patent term after the extension may not exceed 14 years, and only one patent can be extended per product. The application for the extension must be submitted prior to the expiration of the patent, and for patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

### ***FDA Regulation of Companion Diagnostics***

If use of an in vitro diagnostic is essential to safe and effective use of a drug product, then the FDA generally will require approval or clearance of the diagnostic, known as a companion diagnostic, at the same time that the FDA approves the drug product. FDA has generally required manufacturers of in vitro companion diagnostics intended to select the patients who will respond to cancer treatment to submit a pre-market approval application, or PMA, for that diagnostic device simultaneously with the submission of the drug approval application by the drug manufacturer (which may be the same company as the device manufacturer or a different company). The review of these in vitro companion diagnostics in conjunction with the review of a cancer therapeutic involves coordination of review by the FDA's Center for Drug Evaluation and Research and by the FDA's Center for Devices and Radiological Health. Approval and clearance of a companion diagnostic also requires a high level of coordination between the drug manufacturer and device manufacturer, if different companies.

The PMA process, including the gathering of extensive clinical and preclinical data and device manufacturing information, as well as the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with test data and other information to demonstrate reasonable assurance of the device's safety and effectiveness for its intended use, along with information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to a substantial application fee, which is typically increased annually.

In addition, PMAs must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, the applicant must demonstrate that the diagnostic has adequate sensitivity and specificity, has adequate specimen and reagent stability, and produces reproducible results when the same sample is tested multiple times by multiple users at multiple laboratories. As part of the PMA review, the FDA will inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes good manufacturing practice requirements for medical devices, including requirements for established processes, controls, recordkeeping, reporting, documentation and other quality assurance activities.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or submission of specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for

the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also register each of their establishment(s) engaged in manufacturing or initial importation activities, including payment of an annual establishment registration fee, and list the device(s) at each such establishment with the FDA. A medical device manufacturer's design and manufacturing processes and those of its contract manufacturers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Device manufacturers also have post-market reporting requirements for certain types of adverse events and device malfunctions, as well as for device correction and removal activities (including recalls). Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

### ***Other Healthcare Laws***

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain general business and marketing practices in the pharmaceutical industry. These laws include anti-kickback, false claims, transparency and health information privacy laws and other healthcare laws and regulations.

The federal Anti-Kickback Statute is a criminal statute that prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The term "remuneration" has been interpreted broadly to include anything of value. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce or reward referrals of federal healthcare program business, including purchases of products paid by federal healthcare programs, the statute has been violated. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the ACA, amended the intent element of the federal statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to commit a violation. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors - once implemented - are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny and enforcement action if they do not qualify for an exception or safe harbor. Additionally, the ACA amended the federal Anti-Kickback Statute such that a violation of that statute is a basis for liability under the federal civil False Claims Act. The Beneficiary Inducement Civil Monetary Penalties Law imposes similar restrictions on interactions between the biopharmaceutical industry and federal healthcare program beneficiaries.

Federal civil and criminal false claims laws, including the federal civil False Claims Act, prohibit any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid, or avoiding, decreasing or concealing an obligation to pay money to the federal government. Intent to deceive is not required to establish liability under the civil False Claims Act. Rather, a claim may be false for deliberate ignorance of the truth or falsity of the information provided or for acts in reckless disregard of the truth or falsity of that information. Civil False Claims Act actions may be brought by the government or may be brought by private individuals on behalf of the government, called "qui tam" actions. If the government decides to intervene in a qui tam action and prevails in the lawsuit, the individual will share in the proceeds from any damages, penalties or settlement funds. If the government declines to intervene, the individual may pursue the case alone. The civil False Claims Act provides for treble damages and a civil penalty for each false claim, such as an invoice or pharmacy claim for reimbursement, which can aggregate into tens and even hundreds of millions of dollars. For these reasons, since 2004, False Claims Act lawsuits against biopharmaceutical companies have increased significantly in volume and breadth, leading to several substantial global civil and criminal settlements of as much as \$3.0 billion regarding certain sales and promotional practices.

The civil False Claims Act has been used to assert liability on the basis of claims made to programs where the federal government reimburses, such as Medicare and Medicaid, as well as programs where the federal government is a direct



purchaser, such as when it purchases off the Federal Supply Schedule. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates and rebates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Private payers have been filing follow-on lawsuits alleging fraudulent misrepresentation, although establishing liability and damages in these cases is more difficult than under the False Claims Act. Most states also have statutes or regulations similar to the federal Anti-Kickback Statute and civil False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Other federal statutes pertaining to healthcare fraud and abuse include the civil monetary penalties statute, which prohibits, among other things, the offer or payment of remuneration to a Medicaid or Medicare beneficiary that the offeror or payor knows or should know is likely to influence the beneficiary to order a receive a reimbursable item or service from a particular supplier, and the additional federal criminal statutes created by the Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits, among other things, knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program or obtain by means of false or fraudulent pretenses, representations or promises any money or property owned by or under the control of any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items or services.

In addition, we may be subject to healthcare data privacy and security regulations promulgated by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic And Clinical Health Act, (“HITECH Act”), and their respective implementing regulations, impose certain requirements on covered entities relating to the privacy, security, and transmission of certain individually identifiable health information known as protected health information. The HIPAA privacy regulations impose certain requirements with respect to the disclosure of protected health information for research purposes, such as clinical trials. Among other things, the HITECH Act and its implementing regulations, made HIPAA’s security standards and certain privacy standards directly applicable to business associates, defined as persons or organizations, other than members of a covered entity’s workforce, that create, receive, maintain or transmit protected health information on behalf of a covered entity for a function or activity regulated by HIPAA. The HITECH Act also strengthened the civil and criminal sanctions that may be imposed against covered entities, business associates, and individuals, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions. Other federal and state laws, such as the California Consumer Privacy Act (“CCPA”) and Washington’s My Health My Data Act, may govern the privacy and security of health and other information in certain circumstances, many of which differ from each other in significant ways and may not be preempted by HIPAA, thus complicating compliance efforts. Since the CCPA was signed into law in 2018, several other states, including Virginia, Colorado, Utah and Connecticut, have enacted similar privacy laws that may apply to personal information that we collect or maintain.

Further, pursuant to the ACA, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule that requires certain manufacturers of prescription drugs, medical devices and medical products to collect and annually report information on certain payments or transfers of value to U.S.-licensed physicians, as defined by such law, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. The reported data is made available in searchable form on a public website on an annual basis. Failure to submit timely, accurate and complete required information may result in civil monetary penalties. Beginning calendar year 2021, manufacturers must collect information regarding payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiologist assistants and certified nurse- midwives for reporting in 2022. The reported information is made publicly available on a searchable website.

We may also be subject to analogous state and foreign anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, or that apply regardless of payor. In addition, several states now require prescription drug companies to report certain expenses relating to the marketing and promotion of drug products to report gifts and payments to individual healthcare practitioners to prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals, and/or to comply with certain compliance requirements.

Some states require the reporting of certain drug pricing information, including information pertaining to and justifying price increases. In addition, certain states require pharmaceutical companies to implement compliance programs and/or marketing codes. Several additional states are considering similar proposals. Certain states and local jurisdictions also require the registration of pharmaceutical sales representatives. Compliance with these laws is difficult and time consuming, and

companies that do not comply with these state laws face civil penalties. Additionally, we may also be subject to state and foreign laws governing 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.

Efforts to ensure that business arrangements with third parties comply with applicable healthcare laws and regulations involve substantial costs. If a drug company's operations are found to be in violation of any such requirements, it may be subject to significant sanctions, including civil and administrative penalties and damages, criminal fines and confinement, disgorgement, the curtailment or restructuring of its operations, loss of eligibility to obtain approvals from the FDA, exclusion from participation in federal health care programs, suspension and debarment from government procurement and non-procurement programs, refusal of orders under existing government contracts, integrity oversight and reporting obligations, and reputational harm. Although effective compliance programs can mitigate the risk of investigation and enforcement actions for violations of these laws, these risks cannot be entirely eliminated. Any action for an alleged or suspected violation can cause a drug company to incur significant legal expenses and divert management's attention from the operation of the business, even if such action is successfully defended.

### ***U.S. Healthcare Reform***

In the United States there have been, and continue to be, proposals by the federal government, state governments, regulators and third-party payors to control or manage the increased costs of health care and, more generally, to reform the U.S. healthcare system. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, in March 2010, the ACA was enacted, which intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The ACA substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, (i) subjected therapeutic biologics to potential competition by lower-cost biosimilars by creating a licensure framework for follow-on biologic products, (ii) proscribed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs and therapeutic biologics that are inhaled, infused, instilled, implanted or injected, (iii) increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, (iv) established annual nondeductible fees and taxes on manufacturers of certain branded prescription drugs and therapeutic biologics, apportioned among these entities according to their market share in certain government healthcare programs, (v) established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (now 70%) point-of-sale discounts off negotiated prices of applicable brand drugs and therapeutic biologics to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs and therapeutic biologics to be covered under Medicare Part D, (vi) expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability, (vii) expanded the entities eligible for discounts under the Public Health program, (viii) created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research, and (ix) established a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. There have been legislative and judicial efforts to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. We cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted to reduce healthcare expenditures. United States federal government agencies also currently face potentially significant spending reductions, which may further impact healthcare expenditures. On August 2, 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. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030 unless additional Congressional action is taken. The CARES Act, which was signed into law in March 2020 and is designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester through 2031. The

Consolidated Appropriations Act, 2021 extended the suspension of the 2% Medicare sequester through March 31, 2021. Moreover, on January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. If federal spending is further reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

Recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing and price increases, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

The Trump and Biden administrations both issued executive orders intended to favor and encourage domestic manufacturing. And on August 16, 2022, President Biden signed into the law the Inflation Reduction Act of 2022, or the IRA. Among other things, the IRA has multiple provisions that may impact the prices of drug products, such as negotiated ceiling prices and penalties for price increases that exceed the rate of inflation, that are both sold into the Medicare program and throughout the United States.

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 rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. CMS also published an interim final rule that establishes an MFN Model for Medicare Part B drug payment. This regulation would substantially change the drug reimbursement landscape as it bases Medicare Part B payment for 50 selected drugs on prices in foreign countries instead of ASP and establishes a fixed add-on payment in place of the current 6% (4.3% after sequestration) of average sales price, or ASP.

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 or caps, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing.

### ***Coverage and Reimbursement***

Patients in the United States and elsewhere generally rely on third-party payors to reimburse part or all of the costs associated with their prescription drugs. Accordingly, market acceptance of our drug products is dependent on the extent to which third-party coverage and reimbursement is available from government health administration authorities (including in connection with government healthcare programs, such as Medicare and Medicaid in the United States), private healthcare insurers and other healthcare funding organizations. Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we may obtain regulatory approval. Coverage decisions may not favor new drug products when more established or lower-cost therapeutic alternatives are already available. Patients are unlikely to use our products unless reimbursement is adequate to cover all or a significant portion of the cost of our drug products.

Coverage and reimbursement policies for drug products can differ significantly from payor to payor as there is no uniform policy of coverage and reimbursement for drug products among third-party payors in the United States, although private payors often, but not always, follow CMS's decisions regarding coverage and reimbursement. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time-consuming and costly which will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage or adequate reimbursement will be obtained. It is difficult to predict at this time what government authorities and third-party payors will decide with respect to coverage and reimbursement for our drug products. Additionally, we may develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. We, or our collaborators, if any, will be required to obtain coverage and

reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved.

The market for our product candidates will depend significantly on access to third-party payors' drug formularies or lists of medications for which third-party payors provide coverage and reimbursement. Competition to be included in such formularies often leads to downward pricing pressures. In particular, third-party payors may refuse to include a particular reference listed drug in their formularies or otherwise restrict patient access to a reference listed drug when a less costly generic equivalent or other alternative is available.

The U.S. government, state legislatures and foreign governmental entities have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and coverage and requirements for substitution of generic products for branded prescription drugs. Adoption of government controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures could exclude or limit our drugs products from coverage and limit payments for pharmaceuticals.

In addition, we expect that the increased emphasis on managed care and cost containment measures in the United States by third-party payors and government authorities to continue, which will place pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

### ***Employees***

As of December 31, 2023, we had 128 full-time employees. Of our employees, 49% have an M.D. or a Ph.D. From time to time, we also retain independent contractors to support our organization. None of our employees are represented by a labor union or covered by collective bargaining agreements, and we believe our relationship with our employees is good.

### **Corporate Information**

We were incorporated under the laws of the State of Delaware in 2016. Our principal executive offices are located in Wilmington, DE. Our website address is [www.preludetx.com](http://www.preludetx.com). Website references in this Annual Report on Form 10-K are inactive, textual references only, and the information contained on, or that can be accessed through, our website is not part of, and is not incorporated by reference into, this Annual Report on Form 10-K.

The mark "Prelude Therapeutics," the Prelude logo and all product names are our common law trademarks. All other service marks, trademarks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners. Solely for convenience, the trademarks and tradenames referred to in this Annual Report on Form 10-K appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

### **Available Information**

We file our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, electronically with the U.S. Securities and Exchange Commission, or the SEC. The SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is <http://www.sec.gov>.

We make available free of charge electronic versions of our Annual Report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports on our website, [preludetx.com](http://www.preludetx.com), as soon as reasonably practicable after we electronically file or furnish such materials to the Securities and Exchange Commission, or SEC.

## Item 1A. Risk Factors

### RISK FACTORS

*Investing in our common stock involves a high degree of risk. Before making your decision to invest in shares of our common stock, you should carefully consider the risks and uncertainties described below, together with the other information contained in this Annual Report on Form 10-K, including our financial statements and the related notes and “Management’s Discussion and Analysis of Financial Condition and Results of Operations”. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. The occurrence of any of the following risks, or of additional risks and uncertainties not presently known to us or that we currently believe to be immaterial, could materially and adversely affect our business, financial condition, results of operations and prospects. If that were to happen, the trading price of our common stock could decline, and you could lose all or part of your investment.*

#### Summary of Risk Factors

Our business is subject to several risks and uncertainties, including those immediately following this summary. Some of these risks are:

- We have incurred significant operating losses since our inception. We expect to incur continued losses for the foreseeable future and may never be profitable.
- We have never generated any revenue and our inability to execute on our business plan may cause you the total or partial loss of your investment.
- As we do not generate any revenue, we are dependent on working capital to fund our business plan, and we will require substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed or on terms acceptable to us, we could be forced to delay, reduce or eliminate our research or drug development programs, any future commercialization efforts or other operations.
- We are highly dependent on the success of our product candidates which are in early clinical development. We have not completed successful late-stage pivotal clinical trials or obtained regulatory approval for any product candidate. We may never obtain approval for any of our product candidates or achieve or sustain profitability.
- We may incur additional costs or experience delays in completing, or ultimately be unable to complete the development and/or commercialization of our product candidates.
- If we experience delays or difficulties in enrolling patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approval could be delayed or prevented.
- Adverse side effects or other safety risks associated with our product candidates could delay or preclude approval, cause us to suspend or discontinue clinical trials or abandon further development, limit the commercial profile of an approved product, or result in significant negative consequences following marketing approval, if any.
- 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.
- Health care policy changes, including U.S. health care reform legislation, may have a material adverse effect on our business.
- We rely, and intend to continue to rely, on third parties to conduct our clinical trials and perform some of our research and preclinical studies. If these third parties do not satisfactorily carry out their contractual duties, fail to comply with applicable regulatory requirements or do not meet expected deadlines, our development programs may be delayed or subject to increased costs or we may be unable to obtain regulatory approval, each of which may have an adverse effect on our business, financial condition, results of operations and prospects.
- Manufacturing pharmaceutical products is complex and subject to product loss for a variety of reasons. We rely on third-party suppliers, including single source suppliers, to manufacture preclinical and clinical supplies of our product candidates and we intend to rely on third parties to produce commercial supplies of any approved product candidate. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

- We may enter into collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.
- The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue potential and ability to achieve profitability will be adversely affected.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.
- Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.
- Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel and manage our human capital.
- We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.
- Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business.
- We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.
- If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, third parties, including our competitors, could develop and commercialize products similar or identical to ours, and our ability to commercialize our product candidates successfully may be adversely affected.
- We may become involved in lawsuits or administrative disputes to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.
- We may not be able to effectively protect or enforce our intellectual property and proprietary rights throughout the world.
- If we are sued for infringing, misappropriating or otherwise violating intellectual property or proprietary rights of third parties, such litigation or disputes could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.
- Rights to improvements to our product candidates may be held by third parties.
- An active and liquid trading market for our common stock may never be sustained. As a result, you may not be able to resell your shares of common stock at or above the purchase price.
- The market price of our common stock has been and is likely to be highly volatile, which could result in substantial losses for purchasers of our common stock.
- Our principal stockholders and management own a significant percentage of our stock and are able to exert significant control over matters subject to stockholder approval.
- We are an “emerging growth company” and a “smaller reporting company” and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies or smaller reporting companies will make our common stock less attractive to investors.
- We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

## **Risks Related to Our Financial Position and Need for Capital**

***We have incurred significant operating losses since our inception. We expect to incur continued losses for the foreseeable future and may never be profitable.***

Investment in drug development is a highly speculative undertaking and involves a substantial degree of risk. For the year ended December 31, 2023, we reported a net loss of \$121.8 million. As of December 31, 2023, we had an accumulated deficit of \$456.4 million. We have not yet commercialized any product, and we do not expect to generate revenue from sales of any products for several years, if at all. We expect to continue to incur significant research and development and other expenses related to our ongoing operations.

Since our inception, we have focused substantially all of our efforts and financial resources on the research, preclinical and clinical development of our product candidates, and our research efforts on other potential product candidates targeting PRMT5, MCL1, CDK9, and BRM, otherwise known as SMARCA2. As of December 31, 2023, our cash, cash equivalents, and marketable securities were \$232.9 million.

We expect to incur increasing levels of operating losses for the foreseeable future, particularly as we advance our product candidates through clinical development. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses to significantly increase in connection with our additional planned clinical trials for our lead product candidates and the development and subsequent INDs of other future product candidates we may choose to pursue. In addition, if we obtain marketing approval for any of our product candidates, we will incur significant sales, marketing and outsourced manufacturing expenses in connection with the commercialization. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis. We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

***We have never generated any revenue and our inability to execute on our business plan may cause you the total or partial loss of your investment***

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval for, and begin to sell, one or more of our product candidates. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- complete successful Phase 1 clinical trials for our product candidates;
- initiate and successfully complete all safety, pharmacokinetic and other studies required to obtain U.S. and foreign marketing approval for our product candidates;
- initiate and complete successful later-stage clinical trials that meet their clinical endpoints;
- obtain favorable results from our clinical trials and apply for and obtain marketing approval for our product candidates;
- establish licenses, collaborations, or strategic partnerships that may increase the value of our programs;
- successfully manufacture or contract with others to manufacture our product candidates;
- commercialize our product candidates, if approved, by building a sales force or entering into collaborations with third parties;
- submit INDs for a kinase inhibitor that is made effective by the FDA;
- obtain, maintain, protect and defend our intellectual property portfolio; and
- achieve market acceptance of our successful product candidates with the medical community and with third-party payors.

To become and remain profitable, we must succeed in designing, developing, and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials for our product candidates, designing additional product candidates, establishing arrangements with third parties for the manufacture of clinical supplies of our product candidates, obtaining marketing approval for our product candidates and manufacturing, marketing and selling any products for which we may obtain marketing approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

In cases where we are successful in obtaining regulatory approval to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement, and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses we will incur or when, or if, we will be able to achieve profitability. If we decide to or are required by the FDA or regulatory authorities in other jurisdictions to perform studies or clinical trials in addition to those currently expected, or if there are any delays in establishing appropriate manufacturing arrangements for, in initiating or completing our current and planned clinical trials for, or in the development of, any of our product candidates, our expenses could increase materially and profitability could be further delayed.

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 offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

***As we do not generate any revenue, we are dependent on working capital to fund our business plan, and we will require substantial additional funding to pursue our business objectives. If we are unable to raise capital when needed or on terms acceptable to us, we could be forced to delay, reduce or eliminate our research or drug development programs, any future commercialization efforts or other operations.***

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our product candidates through clinical development, and seek to design additional product candidates from our discovery programs. We expect increased expenses as we continue our research and development, expand our operations and complete construction on our new facility, initiate additional clinical trials, and seek marketing approval for our lead programs and our other product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Adequate additional financing may not be available to us on favorable terms, or at all. 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. If we are unable to raise capital when needed or on favorable terms, we could be forced to delay, reduce or eliminate our research and development programs, our commercialization plans or other operations.

We believe that our existing cash, cash equivalents, and marketable securities will enable us to fund our operating expenses, and capital expenditure requirements into 2026. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Changes beyond our control may occur that would cause us to use our available capital before that time, including changes in and progress of our drug development activities and changes in regulation. Our future capital requirements will depend on many factors, including:

- the progress, timing and results of preclinical studies and clinical trials for our current or any future product candidates;
- the extent to which we develop, in-license or acquire other pipeline product candidates or technologies;
- the number and development requirements of other product candidates that we may pursue, and other indications for our current product candidates that we may pursue;



- the costs, timing and outcome of obtaining regulatory approvals of our current or future product candidates and any companion diagnostics we may pursue;
- the scope and costs of making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our current or future product candidates;
- the costs involved in growing our organization to the size needed to allow for the research, development and potential commercialization of our current or future product candidates;
- the cost associated with commercializing any approved product candidates, including establishing sales, marketing and distribution capabilities;
- the cost associated with completing any post-marketing studies or trials required by the FDA or other regulatory authorities;
- the revenue, if any, received from commercial sales of our product candidates that receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims that we may become subject to, including any litigation costs and the outcome of such litigation;
- the costs associated with potential product liability claims, including the costs associated with obtaining insurance against such claims and with defending against such claims; and
- to the extent we pursue strategic collaborations, including collaborations to commercialize our product candidates, our ability to establish and maintain collaborations on favorable terms, if at all, as well as the timing and amount of any milestone or royalty payments we are required to make or are eligible to receive under such collaborations, if any.

We will require additional capital to complete our planned clinical development programs for our current product candidates to obtain regulatory approval. Our ability to raise additional funds will depend on financial, economic and market conditions and other factors, over which we may have no or limited control. If adequate funds are not available on commercially acceptable terms when needed, we may be forced to delay, reduce or terminate the development or commercialization of all or part of our research programs or product candidates or we may be unable to take advantage of future business opportunities. Furthermore, any additional capital-raising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our current and future product candidates, if approved.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to continue to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. 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. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts or grant rights to third parties to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

***Unstable market, economic and political conditions may have serious adverse consequences on our business, financial condition, results of operations and prospects.***

Our business, financial condition, results of operations and prospects could be adversely affected by general conditions in the global economy and in the global financial markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, service providers, manufacturers or other partners and there is a risk that one or more would not survive or be able to meet their commitments to us under such circumstances. As widely reported, global credit and financial markets have experienced volatility and disruptions in the past several years and especially in 2020, 2021 and 2022 due to the impacts of the COVID-19 pandemic, and, more recently, the ongoing conflicts in Ukraine and Israel, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, inflation, increases in unemployment rates and uncertainty about economic stability. There can be no assurances that further deterioration in credit and financial markets and confidence in economic conditions will not occur. For example, U.S. debt ceiling and budget deficit concerns have increased the possibility of additional credit-rating downgrades and economic slowdowns, or a recession in the United States. Although U.S. lawmakers passed legislation to raise the federal debt ceiling on multiple occasions, including a suspension of the federal debt ceiling in June 2023, ratings agencies have lowered or threatened to lower the long-term sovereign credit rating of the United States. The impact of this or any further downgrades to the U.S. government's sovereign credit rating or its perceived creditworthiness could adversely affect the U.S. and global financial markets and economic conditions. 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.

**Risks Related to Design and Development of our Product Candidates**

***We are highly dependent on the success of our product candidates which are in early clinical development. We have not completed successful late-stage pivotal clinical trials or obtained regulatory approval for any product candidate. We may never obtain approval for any of our product candidates or achieve or sustain profitability.***

Our future success is highly dependent on our ability to obtain regulatory approval for, and then successfully commercialize, our product candidates. We are early in our development efforts and our lead product candidates are each currently in a Phase I clinical trial. Our other product candidates are in earlier stages of development. We currently have no products that are approved for sale in any jurisdiction. There can be no assurance that our product candidates in development will achieve success in their clinical trials or obtain regulatory approval. Regulators may also request additional studies, data, and information, that we may need to develop and which were not originally planned. Any delays in obtaining regulatory approval, or if we never obtain regulatory approval, could have a material adverse effect on our business, financial condition and results of operations.

The success of our product candidates will depend on several factors, including the following:

- successful completion of preclinical studies and clinical trials;
- acceptance of INDs by the FDA or other similar clinical trial applications from foreign regulatory authorities for our future clinical trials for our pipeline product candidates;
- timely and successful enrollment of patients in, and completion of, clinical trials with favorable results;
- demonstration of safety, efficacy and acceptable risk-benefit profiles of our product candidates to the satisfaction of the FDA and foreign regulatory agencies;
- our ability, or that of our collaborators, to develop and obtain clearance or approval of companion diagnostics, on a timely basis, or at all;
- receipt and related terms of marketing approvals from applicable regulatory authorities, including the completion of any required post-marketing studies or trials;
- raising additional funds necessary to complete clinical development of and commercialize our product candidates;
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates;
- making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our product candidates;

- developing and implementing marketing and reimbursement strategies;
- establishing sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining third-party payor coverage and adequate reimbursement;
- protecting and enforcing our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of the products following approval and compliance with any post-approval requirements and commitments, including REMS and post-approval studies required by FDA.

Many of these factors are beyond our control, and it is possible that none of our product candidates will ever obtain regulatory approval even if we expend substantial time and resources seeking such approval. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. For example, our business could be harmed if results of our ongoing clinical trials vary adversely from our expectations.

***Drug development involves a lengthy and expensive process, and clinical testing is uncertain as to the outcome.***

We currently have three product candidates in Phase 1 clinical development and additional product candidates in preclinical development, and the risk of failure for each is high. We are unable to predict when or if our product candidates will prove effective or safe in humans or will obtain marketing approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to the outcome.

A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials or of clinical trials of the same product candidates in other indications, and interim or preliminary results of a clinical trial do not necessarily predict final results. Later-stage clinical trials could differ in significant ways from early-stage clinical trials, including changes to inclusion and exclusion criteria, efficacy endpoints, dosing regimen and statistical design. In particular, the small number of patients in our current Phase 1 clinical trials may make the results of these trials less predictive of the outcome of later clinical trials.

***We may incur additional costs or experience delays in completing, or ultimately be unable to complete the development and/or commercialization of our product candidates.***

Before we can initiate clinical trials of a product candidate in any indication, we must submit the results of preclinical studies to the FDA or to comparable foreign authorities, respectively, along with other information, including information about the product candidate's chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND or comparable foreign regulatory filings.

The FDA may require us to conduct additional preclinical studies for any product candidate before it allows us to initiate subsequent clinical trials under any IND, which may lead to additional delays and increase the costs of our preclinical development programs.

Any delays in the commencement or completion of our ongoing, planned or future clinical trials could significantly affect our product development costs. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to obtain marketing approval or commercialize our product candidates, including:

- regulators, IRBs, or ethics committees, or ECs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- the FDA may disagree as to the design or implementation of our clinical trials or with our proposed dose for any of our pipeline programs. For instance, in the oncology space, FDA has recently focused not only on maximum tolerated dose but also on dose optimization, with the issuance of a guidance on this topic. FDA has also expressed

a preference for randomized controlled clinical trials to support accelerated approval, rather than single arm trials with response endpoint;

- delays in reaching, or failure to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective contract research organizations, or CROs, and prospective trial sites;
- clinical trials for our product candidates that may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials, delay or halt clinical trials or abandon product development programs;
- lack of adequate funding to continue the clinical trial;
- the number of patients required for clinical trials for our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or may be lower than we anticipate due to challenges in recruiting and enrolling suitable patients that meet the study criteria, participants may drop out of these clinical trials at a higher rate than we anticipate or the duration of these clinical trials may be longer than we anticipate;
- competition for clinical trial participants from investigational and approved therapies may make it more difficult to enroll patients in our clinical trials;
- difficulties in maintaining contact with patients after treatment, resulting in incomplete data;
- potential failures to obtain regulatory approval of companion diagnostic tests, if required, on a timely basis, or at all;
- potential failures by our third-party contractors to meet their contractual obligations to us in a timely manner, or at all, or failure to comply with regulatory requirements;
- the suspension or termination of clinical trials for our product candidates for various reasons, including a finding by us or by a Data Monitoring Committee for a trial that the participants are being exposed to unacceptable health risks;
- undesirable or unexpected side effects or other unexpected characteristics from our product candidates, causing us or our investigators, regulators or IRBs/ECs to suspend or terminate the trials;
- the cost of clinical trials for our product candidates may be greater than we anticipate;
- changes to clinical trial protocol;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials for our product candidates may be insufficient or inadequate and result in delays or suspension of our clinical trials; and
- the impact recent COVID-19 pandemic, or another widespread outbreak of any other communicable disease, which may slow potential enrollment, reduce the number of eligible patients for clinical trials, or reduce the number of patients that remain in our trials.

Delays, including delays caused by the above factors, can be costly and could negatively affect our ability to complete a clinical trial or obtain timely marketing approvals. We do not know whether any of our planned preclinical studies or clinical trials will begin on a timely basis or at all, will need to be restructured or will be completed on schedule, or at all. For example, the FDA may place a partial or full clinical hold on any of our clinical trials for a variety of reasons, including safety concerns and noncompliance with regulatory requirements. If we are not able to complete successful clinical trials, we will not be able to obtain regulatory approval and will not be able to commercialize our product candidates.

Significant preclinical or clinical trial delays also could 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 and may harm our business and results of operations.

***If we experience delays or difficulties in enrolling patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approval could be delayed or prevented.***

We may not be able to initiate or continue our ongoing or planned clinical trials for our product candidates if we are unable to identify and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or comparable foreign regulatory authorities. In addition, some of our competitors currently have ongoing clinical trials for product candidates that would treat the same patients as our clinical product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- our ability to recruit clinical trial investigators of appropriate competencies and experience;
- the incidence and prevalence of our target indications;
- clinicians' and patients' awareness of, and perceptions as to the potential advantages and risks of our product candidates in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- competing studies or trials with similar eligibility criteria;
- invasive procedures required to enroll patients and to obtain evidence of the product candidate's performance during the clinical trial;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria defined in the protocol for the trial in question;
- the size and nature of the patient population required for analysis of the trial's primary endpoints;
- efforts to facilitate timely enrollment in clinical trials;
- disruptions caused by and the willingness of patients to enroll in a clinical trial during outbreaks of contagious disease;
- whether we are subject to a partial or full clinical hold on any of our clinical trials;
- reluctance of physicians to encourage patient participation in clinical trials;
- the ability to monitor patients adequately during and after treatment;
- our ability to obtain and maintain patient consents; and
- proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll and maintain a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs, which would cause the value of our company to decline and limit our ability to obtain additional financing.

***Adverse side effects or other safety risks associated with our product candidates could delay or preclude approval, cause us to suspend or discontinue clinical trials or abandon further development, limit the commercial profile of an approved product, or result in significant negative consequences following marketing approval, if any.***

Results of our ongoing and planned clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could result in the delay, suspension or termination of clinical trials by us or regulatory authorities for a number of reasons. Furthermore, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of subjects and limited duration of exposure, rare and severe side effects of our product candidates or those of our competitors may only be uncovered with a significantly larger number of patients exposed to the drug.

Additionally, due to the high mortality rates of the cancers for which we are initially pursuing development and the pretreated nature of many patients in our ongoing clinical trials, a material percentage of patients in these clinical trials may die during a trial, which could impact the development of product candidates. If we elect or are required to delay, suspend or terminate any clinical trial, the commercial prospects of our product candidates will be harmed and our ability to generate

product revenues from this product candidate will be delayed or eliminated. Adverse events observed in clinical trials could prevent approval of the product or, if approved, hinder or prevent market acceptance of our product candidates. Any of these occurrences may harm our business, prospects, financial condition and results of operations significantly.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for our product candidates, if approved. We may also be required to modify our study plans based on findings in our clinical trials. Such side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial. Many drugs that initially showed promise in early stage testing have later been found to cause side effects that prevented further development. In addition, regulatory authorities may draw different conclusions, require additional testing to confirm these determinations, require more restrictive labeling, or deny regulatory approval of the product candidate.

It is possible that, as we test our product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens, or as the use of our product candidates becomes more widespread following any regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition, results of operations and prospects significantly.

In addition, if any of our product candidates receive marketing approval, and we or others later identify undesirable side effects caused by treatment with such drug, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approval of the drug;
- we may be required to recall a product or change the way the drug is administered to patients;
- regulatory authorities may require additional warnings in the labeling, such as a contraindication or a boxed warning, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- we may be required to implement a REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- additional restrictions may be imposed on the marketing or promotion of the particular product or the manufacturing processes for the product or any component thereof;
- we could be sued and held liable for harm caused to patients;
- we may be subject to regulatory investigations and government enforcement actions;
- the drug could become less competitive; and
- our reputation may suffer.

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

***Preliminary, interim and topline 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 publicly disclose preliminary, interim or topline data from our clinical trials. These updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. Additionally, 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. Therefore, positive interim results in any ongoing clinical trial may not be predictive of such results in the completed study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the

opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. In addition, we may report interim analyses of only certain endpoints rather than all endpoints. Adverse changes between preliminary or interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock. See the description of risks under the heading “Risks Related to our Common Stock” for more disclosure related to the risk of volatility in our stock price.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. You or others may not agree with what we determine is the material, or otherwise appropriate, information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product, product candidate or our business. If the preliminary or topline data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize any product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

***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.***

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. 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 commercially viable products. 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 royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

***We may not be successful in our efforts to design additional potential product candidates.***

A key element of our strategy is to identify molecular targets and intervention points leading to treatment failure and then apply our expertise of cancer biology and medicinal chemistry, as well as our in-depth understanding of the current landscape of oncology treatments, to design solutions that can be precisely tailored in a target class agnostic fashion. The therapeutic design and development activities that we are conducting may not be successful in developing product candidates that are safe and effective in treating cancer or other diseases. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the target selection methodology used may not be successful in identifying potential product candidates;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will obtain marketing approval or achieve market acceptance; or
- potential product candidates may not be effective in treating their targeted diseases.

Research programs to identify and design new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. If we are unable to identify and design suitable product candidates for preclinical and clinical development, we will not be able to obtain revenues from the sale of products in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

## Risks Related to Government Regulation

*The development and commercialization of pharmaceutical products are subject to extensive regulation, and we may not obtain regulatory approvals for any product candidates, on a timely basis or at all.*

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, import, marketing, distribution, adverse event reporting, including the submission of safety and other post-marketing information and reports, and other possible activities relating to our product candidates are subject to extensive regulation. Marketing approval of drugs in the United States requires the submission of an NDA to the FDA, and we are not permitted to market any product candidate in the United States until we obtain approval from the FDA of the NDA for that product. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. Our product candidates must be approved by comparable regulatory authorities in other jurisdictions prior to commercialization.

FDA approval of an NDA is not guaranteed, and the review and approval process is an expensive and uncertain process that may take several years. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, there can be no assurance that any of our product candidates will receive regulatory approval in the United States, or other jurisdictions.

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 NDA 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 results of preclinical and early clinical trials of any product candidate may not be predictive of the results of our later-stage clinical trials.

Clinical trial failure may result from a multitude of factors including flaws in trial design, dose selection, placebo effect, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits, and failure in clinical trials can occur at any stage. Companies in the pharmaceutical industry frequently suffer setbacks in the advancement of clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Based upon negative or inconclusive results, we may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. In addition, data obtained from clinical trials are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may further delay, limit or prevent marketing approval.

The FDA could delay, limit or deny approval of a product candidate for many reasons, including because the FDA:

- may not deem our product candidate to be safe and effective;
- determines that the product candidate does not have an acceptable benefit-risk profile;
- determines, in the case of an NDA seeking accelerated approval, that the NDA does not provide evidence that the product candidate represents a meaningful advantage over available therapies;
- determines that the objective response rate, or ORR, and duration of response are not clinically meaningful;
- may require that we do additional work to determine the optimal dose;
- may not agree that the data collected from preclinical studies and clinical trials are acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval and may impose requirements for additional preclinical studies or clinical trials;
- may determine that adverse events experienced by participants in our clinical trials represent an unacceptable level of risk;
- may determine that population studied in the clinical trial may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- may not accept clinical data from trials, which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States;
- may disagree regarding the formulation, labeling and/or the specifications;
- may not approve the manufacturing processes associated with our product candidate or may determine that a manufacturing facility does not have an acceptable compliance status;



- may change approval policies or adopt new regulations; or
- may not file a submission due to, among other reasons, the content or formatting of the submission.

In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials, and the review process. For example, the Oncology Center of Excellence, or OCE, within the FDA has recently advanced Project Optimus, which is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development to emphasize selection of an optimal dose, which is a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well. This shift from the prior approach, which generally determined the maximum tolerated dose, may require sponsors to spend additional time and resources to further explore a product candidate's dose-response relationship to facilitate optimum dose selection in a target population. Other recent OCE initiatives have included Project FrontRunner, a new initiative with a goal of developing a framework for identifying candidate drugs for initial clinical development in the earlier advanced setting rather than for treatment of patients who have received numerous prior lines of therapies or have exhausted available treatment options. We are considering these policy changes as they relate to our programs.

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 our clinical product candidates.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, our commercial prospects will be harmed and our ability to generate revenues will be materially impaired which would adversely affect our business, prospects, financial condition and results of operations.

***The accelerated approval pathway for our product candidates may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.***

Under the FDA's accelerated approval program, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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. We may seek accelerated approval for one or more of our product candidates on the basis of ORR with an acceptable duration of response, a surrogate endpoint that we believe is reasonably likely to predict clinical benefit.

For drugs granted accelerated approval, post-marketing confirmatory trials are required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence. By the date of approval of an accelerated approval product, FDA must specify the conditions for the required post approval studies, including enrollment targets, the study protocol, milestones, and target completion dates. FDA may also require that the confirmatory Phase 4 studies be commenced prior to FDA granting a product accelerated approval. Reports on the progress of the required Phase 4 confirmatory studies must be submitted to FDA every 180 days after approval. If the trials fail to verify the clinical benefit of the drug or biologics product, the FDA may withdraw approval of the application through a statutorily defined streamlined process. Failure to conduct the required Phase 4 confirmatory studies or to conduct such studies with due diligence, as well as failure to submit the required update reports can subject a sponsor to penalties.

If any of our competitors were to receive full approval on the basis of a confirmatory trial for an indication for which we are seeking accelerated approval before we receive accelerated approval, the indication we are seeking may no longer qualify as a condition for which there is an unmet medical need and accelerated approval of our product candidate would be more difficult, or impossible, to obtain. Also, the existing treatment landscape may change, which may necessitate that we conduct additional studies or collect additional data to obtain accelerated approval. Moreover, the FDA may withdraw approval of our product candidate approved under the accelerated approval pathway if, for example:

- the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug;

- other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use;
- we fail to conduct any required post-approval trial of our product candidate with due diligence; or
- we disseminate false or misleading promotional materials relating to the relevant product candidate.

Recently, the accelerated approval pathway has come under scrutiny within the FDA and by Congress. The FDA has put increased focus on ensuring that confirmatory studies are conducted with diligence and, ultimately, that such studies confirm the benefit. For example, FDA convened its Oncologic Drugs Advisory Committee to review what the FDA has called dangling or delinquent accelerated approvals where confirmatory studies have not been completed or where results did not confirm benefit. In addition, the OCE has announced Project Confirm, which is an initiative to promote the transparency of outcomes related to accelerated approvals for oncology indications and provide a framework to foster discussion, research and innovation in approval and post-marketing processes, with the goal to enhance the balance of access and verification of benefit for therapies available to patients with cancer and hematologic malignancies. We may see further legislative or regulatory changes to this program in the future.

***Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in those jurisdictions, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.***

In order to market and sell our products in any jurisdiction outside the United States, 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 regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to submit for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

***We may not be able to obtain or maintain orphan drug designation or exclusivity for our product candidates.***

Regulatory authorities in some jurisdictions, including the United States, may designate drugs for relatively small patient populations as “orphan drugs.” Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States, or if the disease or condition affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing the drug for the type of disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. Additionally, if a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years, except in certain circumstances, such as a showing of clinical superiority (i.e., another product is safer, more effective or makes a major contribution to patient care) over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity, or obtain approval for the same product but for a different indication than that for which the orphan product has exclusivity.

We may apply for an orphan drug designation in the United States or other geographies for our product candidates, where such designation is available, in the future. However, obtaining an orphan drug designation can be difficult, and we may not be successful in doing so. Even if we obtain orphan drug designation for our product candidates in specific indications, we may not be the first to obtain regulatory approval of these product candidates for the orphan-designated indication, due to the uncertainties associated with developing pharmaceutical products, in which case we may be blocked by other’s periods of regulatory exclusivity or may need to demonstrate clinical superiority, which we may not be able to do. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than

the orphan-designated indication or may be lost if the FDA later determines that the request for orphan designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Orphan drug designation does not ensure that we will receive marketing exclusivity in a particular market, and we cannot assure you that any future application for orphan drug designation in any other geography or with respect to any other product candidate will be granted. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process.

***A Breakthrough Therapy Designation by the FDA for any of our current or future product candidates may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that the product candidate will receive marketing approval.***

We may seek a Breakthrough Therapy Designation for one or more of our current or future product candidates. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug 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 drugs 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. Drugs designated as breakthrough therapies by the FDA are also eligible for priority review if supported by clinical data at the time of the submission of the NDA.

Designation as a breakthrough therapy is at the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a drug may not result in a faster development process, review, or approval compared to drugs considered for approval under conventional FDA procedures and it would not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidate no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened.

***If we are unable to successfully develop, validate, obtain regulatory approval of and commercialize companion diagnostic tests for any product candidates that require such tests, or experience significant delays in doing so, we may not realize the full commercial potential of these product candidates.***

A companion diagnostic is a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding therapeutic drug product. A companion diagnostic can be used to identify patients who are most likely to benefit from the therapeutic product. In the future, we may evaluate opportunities to develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications.

A companion diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product. To date, the FDA has required premarket approval of the vast majority of companion diagnostics for cancer therapies. Generally, when a companion diagnostic is essential to the safe and effective use of a drug product, the FDA requires that the companion diagnostic be approved before or concurrent with approval of the therapeutic product and before a product can be commercialized. The approval of a companion diagnostic as part of the therapeutic product's labeling limits the use of the therapeutic product to only those patients who express the specific genetic alteration that the companion diagnostic was developed to detect.

Development of a companion diagnostic could include additional meetings with regulatory authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption application. In the case of a companion diagnostic that is designated as a "significant risk device," approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate.

To be successful in developing, validating, obtaining approval of and commercializing a companion diagnostic, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for companion diagnostic tests on our own, we will require additional personnel. We may rely on third parties for the design, development, testing, validation and manufacture of companion diagnostic tests for our therapeutic product candidates that

require such tests, the application for and receipt of any required regulatory approvals, and the commercial supply of these companion diagnostics. If these parties are unable to successfully develop companion diagnostics for these therapeutic product candidates, or experience delays in doing so, we may be unable to enroll enough patients for our current and planned clinical trials, the development of these therapeutic product candidates may be adversely affected, these therapeutic product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of these therapeutics that obtain marketing approval. For any product candidate for which a companion diagnostic is necessary to select patients who may benefit from use of the product candidate, any failure to successfully develop a companion diagnostic may cause or contribute to delayed enrollment of our clinical trials, and may prevent us from initiating a pivotal trial. In addition, the commercial success and approval of any of our product candidates that require a companion diagnostic will be tied to and dependent upon the receipt of required regulatory approvals and the continued ability of such third parties to make the companion diagnostic commercially available to us on reasonable terms in the relevant geographies. Any failure to do so could materially harm our business, results of operations and financial condition.

***If we decide to pursue a Fast Track Designation by the FDA, it may not lead to a faster development or regulatory review or approval process.***

We may seek Fast Track Designation for one or more of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the product sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

***Even if we obtain marketing approval for our product candidates, the terms of approvals, ongoing regulation of our products or other post-approval restrictions may limit how we manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.***

Any product candidates for which we receive accelerated approval from the FDA are required to undergo one or more confirmatory clinical trials. If such a product candidate fails to meet its safety and efficacy endpoints in such confirmatory clinical trials, the regulatory authority may withdraw its conditional approval. There is no assurance that any such product will successfully advance through its confirmatory clinical trial(s). Therefore, even if a product candidate receives accelerated approval from the FDA, such approval may be withdrawn at a later date.

Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, which may include the requirement to implement a REMS or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product.

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 drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling, among other requirements. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to ensure that quality control and manufacturing procedures conform to cGMPs which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our CMOs could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

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

***Any product candidate for which we obtain marketing approval will be subject to ongoing enforcement of post-marketing requirements by regulatory agencies, and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.***

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding drug distribution and the distribution of samples to physicians and recordkeeping.

The FDA and other federal and state agencies, including the Department of Justice, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. For example, 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. Violations of such requirements may lead to investigations alleging violations of the Federal Food, Drug, and Cosmetic Act, or FDCA, and other statutes, including the False Claims Act and other federal and state healthcare fraud and abuse laws as well as state consumer protection laws. Our failure to comply with all regulatory requirements either before or after approval, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

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

Non-compliance by us or any future collaborator with regulatory requirements, including safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population can also result in significant financial penalties.

***Our current and future relationships with customers and third-party payors may be subject to applicable anti-kickback, fraud and abuse, transparency, health privacy, and other healthcare laws and regulations, which could expose us to significant sanctions, including criminal, civil, and administrative penalties, contractual damages, reputational harm and diminished profits and future earnings.***

Healthcare providers, including physicians, and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research, as well as, market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations that may be applicable to our business include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, 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 a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the federal civil False Claims Act, which can be enforced by individual whistleblowers in “qui tam” actions brought on behalf of the government, and criminal false claims laws and the civil monetary penalties law, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, regardless of the payor (*e.g.*, public or private), and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates and their 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 such individually identifiable health information;
- the federal transparency reporting requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to annually report to the Centers for Medicare & Medicaid Services, or CMS, information related to certain payments and other transfers of value provided to teaching hospitals and to U.S.-licensed physicians, (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and anesthesiologist assistants, and certified nurse-midwives. Applicable manufacturers also most report ownership and investment interests held by physicians and their immediate family members; and
- analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines or the Compliance Program Guidelines for Pharmaceutical Manufacturers published by the U.S. Department of Health & Human Services, Office of Inspector General, implement gift bans, and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures, or drug pricing, including price increases. Some state and local laws require the registration of pharmaceutical sales representatives. State and non-U.S. laws that 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.

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

regulations that may apply to us, we may be subject to significant sanctions, including civil and administrative penalties and damages, criminal fines and confinement, disgorgement, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid and other federal healthcare programs, suspension and debarment from government procurement and non-procurement programs, refusal of orders under existing government contracts, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil and administrative sanctions, including exclusion from participation in government funded healthcare programs, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

***Health care policy changes, including U.S. health care reform legislation, may have a material adverse effect on our business.***

In response to perceived increases in health care costs in recent years, there have been and continue to be proposals by the federal government, state governments, regulators, and third-party payors to control these costs and, more generally, to reform the U.S. health care system. Certain of these proposals could limit the prices we are able to charge for our products or the amounts of reimbursement available for our products and could limit the acceptance and availability of our products. Further, while the United States has begun experimenting with pay-for-performance rather than fee-for-service models and has been embracing many shared-risk arrangements, CMS and OIG specifically excluded manufacturers and others from utilizing the new, more flexible Stark Law exceptions and Anti-Kickback Statute safe harbors for value-based care under the Final Rules, part of the U.S. Department of Health and Human Services' Regulatory Sprint to Coordinated Care, which were published on December 2, 2020 in the Federal Register and were largely effective January 19, 2021. The exclusion of manufacturers from utilizing these exceptions and safe harbors will not allow us to avail ourselves of immunity from liability under the laws, potentially inviting greater scrutiny over our shared risk arrangements.

Comprehensive healthcare legislation, signed into law in the United States in March 2010, titled the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, collectively, the ACA, imposes certain stringent compliance, recordkeeping, and reporting requirements on companies in various sectors of the life sciences industry, and enhanced penalties for non-compliance. Despite the ACA going into effect over a decade ago, there have been numerous legal and Congressional challenges to the law's provisions and the effect of certain provisions have made compliance costly.

We cannot predict what additional new legislation, agency priorities, and rulemakings may be on the horizon as the United States continues to reassess how it pays for healthcare. As a result, we cannot quantify or predict what impact any changes might have on our business and results of operations. However, any changes that restrict coverage or lower reimbursement for our products could materially and adversely affect our business, financial condition and results of operations.

Other legal, regulatory and commercial policy influences are subjecting our industry to significant changes, and we cannot predict whether new regulations or policies will emerge from U.S. federal or state governments, foreign governments, or third-party payors. Government and commercial payors may, in the future, consider healthcare policies and proposals intended to curb rising healthcare costs, including those that could significantly affect reimbursement for healthcare products such as our systems. These policies have included, and may in the future include: basing reimbursement policies and rates on clinical outcomes, the comparative effectiveness, and costs, of different treatment technologies and modalities; imposing price controls and taxes on medical device providers; and other measures. These policies recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the U.S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D. The negotiated prices, which will first become effective in 2026, will be capped at a statutory ceiling price beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. Future significant changes in the healthcare systems in the United States or elsewhere could also have a negative impact on the demand for our current and future products. These include changes that may reduce reimbursement rates for our products and changes that may be proposed or implemented by the current or future laws or regulations.

***Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.***

In some countries, particularly the countries of the European Union, or the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel trade, such as arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products.

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

We currently are subject to a number of government laws and regulations and, in the future, could become subject to new government laws and regulations. The costs of compliance with such laws and regulations, or the negative results of non-compliance, could adversely affect our business, cash flow, results of operations, financial condition and prospects. For example, if we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate, including anti-corruption laws. The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business, and third-party agents acting on their behalf, from paying, offering, or authorizing the payment or offering of anything of value, directly or indirectly, to any foreign official, foreign political party or official thereof, or candidate for foreign political office, for the purpose of influencing any act or decision of such official in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions and disposition of the company's assets, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA's provisions can be costly and challenging, particularly in countries in which corruption is deemed to be a significant risk and in the life sciences industries, where, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials per se. Certain payments to hospitals in connection with clinical trials and other work have been considered improper payments to government officials and led to FCPA enforcement actions with significant fines and penalties.

Various international trade, export control and sanctions laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. persons in the United States, of personal identifying information and products, technology or sensitive personal data controlled for export, as well as restricting our ability to deal with certain persons subject to sanctions. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties for both the company and individuals, as well as possible suspension or debarment from government contracting. The Securities and Exchange Commission, or the SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

***If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.***

We and our third-party contractors are subject to numerous foreign, federal, state and local environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. 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, including any available insurance.

In addition, our leasing and operation of real property may subject us to liability pursuant to certain of these laws or regulations. Under existing U.S. environmental laws and regulations, current or previous owners or operators of real property and entities that disposed or arranged for the disposal of hazardous substances may be held strictly, jointly and severally liable for the cost of investigating or remediating contamination caused by hazardous substance releases, even if they did not know of and were not responsible for the releases.

We could incur significant costs and liabilities which may adversely affect our financial condition and operating results for failure to comply with such laws and regulations, including, among other things, civil or criminal fines and penalties, property damage and personal injury claims, costs associated with upgrades to our facilities or changes to our operating procedures, or injunctions limiting or altering our operations.

Although we maintain liability insurance to cover us for costs and expenses we may incur due to injuries to our employees, 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 connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations, which are becoming increasingly more stringent, may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

#### **Risks Related to Our Reliance on Third Parties**

***We rely, and intend to continue to rely, on third parties to conduct our clinical trials and perform some of our research and preclinical studies. If these third parties do not satisfactorily carry out their contractual duties, fail to comply with applicable regulatory requirements or do not meet expected deadlines, our development programs may be delayed or subject to increased costs or we may be unable to obtain regulatory approval, each of which may have an adverse effect on our business, financial condition, results of operations and prospects.***

We do not have the ability to independently conduct all aspects of our preclinical testing or clinical trials ourselves. As a result, we are dependent on third parties to conduct our ongoing and planned clinical trials of our product candidates and any preclinical studies and clinical trials of any other product candidates. The timing of the initiation and completion of these trials will therefore be partially controlled by such third parties and may result in delays to our development programs. Specifically, we expect CROs, clinical investigators, laboratories and consultants to play a significant role in the conduct of these trials and the subsequent collection and analysis of data. However, these CROs and other third parties are not our employees, and we will not be able to control all aspects of their activities. Nevertheless, we are responsible for ensuring that each clinical trial is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. By example, we are required to monitor the activities of third parties undertaking clinical trials on our behalf, but our monitoring may not be able to detect any existing or emerging issues.

We and our CROs are required to comply with good clinical practices, or GCP, requirements, which are regulations and guidelines enforced by the FDA for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical trial investigators and clinical trial sites. If we or any of our CROs or clinical trial sites fail to comply with applicable GCP requirements or to conduct a trial in accordance with its investigational plan, the data generated in our clinical trials may be deemed unreliable, and the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with product produced under cGMP regulations applicable to the stage of product development and our preclinical trials must be conducted in accordance with good laboratory practices. Our failure or the failure of third parties on whom we rely on to comply with these regulations may require us to stop and/or repeat clinical trials or other studies, which would delay the marketing approval process.

There is no guarantee that any such CROs, clinical trial investigators or other third parties on which we rely will devote adequate time and resources to our development activities or perform as contractually required. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, otherwise perform in a substandard manner, or terminate their engagements with us, the timelines for our development programs may be extended or delayed or our development activities may be suspended or terminated. If our clinical trial site terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in such clinical trial unless we are able to transfer those subjects to another qualified clinical trial site, which may be difficult or impossible.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors for whom they may also be conducting clinical trials or other pharmaceutical product development activities that could harm our competitive position. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products.

***Manufacturing pharmaceutical products is complex and subject to product loss for a variety of reasons. We rely on third-party suppliers, including single source suppliers, to manufacture preclinical and clinical supplies of our product candidates and we intend to rely on third parties to produce commercial supplies of any approved product candidate. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.***

We do not have any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, product development purposes, to support regulatory application submissions, as well as for commercial manufacture if any of our product candidates obtain marketing approval. In addition, we expect to contract with analytical laboratories for release and stability testing of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

We may be unable to establish any agreements with third-party manufacturers or do so on favorable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory, compliance and quality assurance;
- reliance on the third party for product development, analytical testing, and data generation to support regulatory applications;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier, the issuance of an FDA Form 483 notice or warning letter, or other enforcement action by FDA or other regulatory authority;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- carrier disruptions or increased costs that are beyond our control; and
- failure to deliver our drugs under specified storage conditions and in a timely manner.

We have only limited supply arrangements in place with respect to our product candidates, and these arrangements do not extend to commercial supply. We acquire many key materials on a purchase order basis. As a result, we do not have long-term committed arrangements with respect to our product candidates and other materials. We will need to establish one or more agreements with third parties to develop and scale up the drug manufacturing process, conduct drug testing, and generate data to support a regulatory submission. If we obtain marketing approval for any of our product candidates, we will need to establish an agreement for commercial manufacture with a third party.

In addition, we are dependent on a sole supplier for certain components of our manufacturing process. Even if we are able to replace any raw materials or other materials with an alternative, such alternatives may cost more, result in lower yields or not be as suitable for our purposes. In addition, some of the materials that we use to manufacture our product candidates are complex materials, which may be more difficult to substitute. Therefore, any disruptions arising from our sole suppliers could result in delays and additional regulatory submissions.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. While we would not be manufacturing the products ourselves, we will still be responsible for the ultimate quality of any product or product candidate that we put into distribution. If the FDA determines that our CMOs are not in compliance with FDA laws and regulations, including those governing cGMPs, the FDA may deny a new drug application, or NDA, approval until the deficiencies are corrected or we replace the manufacturer in our application with a manufacturer that is in compliance. Moreover, our failure, or the failure of our third-party manufacturers and suppliers, to comply with applicable regulations could result in the need to repeat clinical or preclinical trials, sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products. In addition, approved products and the facilities at which they are manufactured are required to maintain ongoing compliance with extensive FDA requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to cGMP requirements. As such, our CMOs are subject to continual review and periodic inspections to assess compliance with cGMPs. Furthermore, although we do not have day-to-day control over the operations of our CMOs, we are responsible for ensuring compliance with applicable laws and regulations, including cGMPs.

In addition, our third-party manufacturers and suppliers are subject to numerous environmental, health and safety laws and regulations, including those governing the handling, use, storage, treatment and disposal of waste products, and failure to comply with such laws and regulations could result in significant costs associated with civil or criminal fines and penalties for such third parties. Based on the severity of regulatory actions that may be brought against these third parties in the future, our clinical or commercial supply of drug and packaging and other services could be interrupted or limited, which could harm our business.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. As a result, we may not obtain access to these facilities on a priority basis or at all. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

As we prepare for later-stage clinical trials and potential commercialization, we will need to take steps to increase the scale of production of our product candidates. We have not yet scaled up the manufacturing process for any of our product candidates. Third party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up or commercial activities. For example, if microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current CMOs for preclinical and clinical testing cannot perform as agreed, we may be required to replace such CMOs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement manufacturer or be able to reach agreement with any alternative manufacturer. Further, our third-party manufacturers may experience manufacturing or shipping difficulties due to resource constraints or as a result of natural disasters, labor disputes, unstable political environments, including the ongoing conflict in Ukraine, or public health epidemics such as the COVID-19 pandemic. If our current third-party manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that obtain marketing approval on a timely and competitive basis.

***We may enter into collaborations with third parties for the further development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.***

We may seek third-party collaborators for the further development and commercialization of some of our product candidates on a select basis. Our likely collaborators for any future collaboration arrangements include large and mid-size pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators and may not be able to secure an appropriate collaborator. Our ability to reach a definitive agreement for a future collaboration will depend, among other things, upon our assessment of the future collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors.

If we do enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our future collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements. Collaborations with future collaborators involving our product candidates would pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may de-emphasize or 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 collaborators' strategic focus, including as a result of a sale or disposition of a business unit or development function, or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a 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 could independently develop, or develop with third parties, products that compete directly or indirectly with our products or 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;
- a collaborator with marketing and distribution rights to multiple products may not commit sufficient resources to the marketing and distribution of our product relative to other products;
- collaborators may not properly obtain, maintain, defend or enforce our intellectual property rights or may use our proprietary information and intellectual property in such a way as to invite litigation or other intellectual property related proceedings that could jeopardize or invalidate our proprietary information and intellectual property or expose us to potential litigation or other intellectual property related proceedings;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all; and
- if a future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we establish one or more collaborations, all of the risks relating to product development, regulatory approval and commercialization described herein would also apply to the activities of any such future collaborators.

## Risks Related to Commercialization of our Product Candidates

***The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue potential and ability to achieve profitability will be adversely affected.***

The total addressable market opportunity for any product candidates we may develop will ultimately depend upon, among other things, the diagnosis criteria included in the final labeling for each such product candidate if our product candidates are approved for sale for these indications, acceptance by the medical community, patient access, drug and any related companion diagnostic pricing and their reimbursement. We may initially seek regulatory approval of some of our product candidates as therapies for relapsed or refractory patients. The number of patients in our targeted commercial markets and elsewhere may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our drugs, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business.

***Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.***

If any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, current cancer treatments, such as existing targeted therapies, chemotherapy, and radiation therapy, are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates 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 our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the acceptance of our product candidates as front-line treatment for various indications;
- the prevalence and severity of any side effects, in particular compared to alternative treatments;
- limitations or warnings contained in the labeling approved for our product candidates by the FDA;
- the size of the target patient population;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the strength of marketing and distribution support;
- publicity for our product candidates and competing products and treatments;
- the existence of distribution and/or use restrictions, such as through a REMS;
- the availability of third-party payor coverage and adequate reimbursement;
- the timing of any marketing approval in relation to other product approvals;
- support from patient advocacy groups; and
- any restrictions on the use of our products together with other medications.

***We currently have no marketing and sales organization and have no experience as a company in commercializing products and we may have to invest significant resources to develop these capabilities. If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our products, we may not be able to generate revenue.***

We currently have no sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we obtain marketing approval, we will

need to establish sales, marketing and distribution capabilities, either ourselves or through collaboration or other arrangements with third parties.

There are risks involved with establishing our own sales and marketing capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts are expected to be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- our inability to raise financing necessary to build our commercialization infrastructure;
- the inability of sales personnel to obtain access to physicians or educate an adequate number of physicians as to the benefits of our products;
- unfavorable third-party payor coverage and reimbursement in any geography;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales and marketing services, our product revenues and our profitability, if any, are likely to be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to market and sell our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of these third parties may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates for which we receive marketing approval.

***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 pharmaceutical 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 companies, specialty pharmaceutical companies and existing or emerging biotechnology companies, academic research institutions and governmental agencies and public and private research institutions worldwide. There are a number of pharmaceutical and biotechnology companies that currently are pursuing the development of precision oncology therapies optimized to effectively target the key driver mechanisms in cancers with high unmet need, including Arvinas Inc., Aurigene, Black Diamond Therapeutics, Inc., Boehringer Ingelheim, C4 Therapeutics, Constellation Pharmaceuticals, Inc., Eli Lilly and Company, F. Hoffman-La Roche, Foghorn Therapeutics Inc., Fochon Pharmaceuticals, G1 Therapeutics Inc., Genentech, Kronos Bio, Inc., Kura Oncology, Inc., Kymera Therapeutics Inc., Mirati Therapeutics Inc., Nuvation Bio Inc. Repare Therapeutics Inc., Revolution Medicines, Inc., Relay Therapeutics, Inc., Springworks Therapeutics, Inc., Syndax Pharmaceuticals, Inc., and Zentalis Pharmaceuticals, Inc. In addition, we may face competition from companies developing product candidates that are based on targeting pathways of adaptive resistance, including Amgen Inc., AbbVie Inc., AstraZeneca plc, GlaxoSmithKline plc, Ideaya Biosciences, Johnson & Johnson Services, Inc., Pfizer Inc., Tango Therapeutics, Inc., Vincerx Pharma, Inc., Novartis AG, and Gilead Sciences, Inc.

For our MCL1 program, PRT1419, other companies are developing MCL1 inhibitors with monotherapy and/or combination trials ongoing, including Amgen (AMG176), AstraZeneca (AZD5991), Novartis (MIK665), and Gilead (GS-9716). For our CDK9 program, PRT2527, both AstraZeneca (AZD4573), Vincerx (VIP512), and Kronos (KB-0742) have CDK9 programs in Phase 1 clinical trials. For our CDK4/6 program, PRT3645, Novartis (ribociclib), Lilly (abemaciclib), Pfizer (53albociclib), G1 Therapeutics (G1T38), and Fochon Pharmaceuticals (FCN-437) have clinical trials ongoing. For our SMARCA2 (BRM) degrader program, other companies, including Amgen, Aurigene, C4 Therapeutics, F. Hoffmann-La Roche, Foghorn Therapeutics, Inc., Kymera Therapeutics, Arvinas, Genentech, Boehringer Ingelheim, and Lilly have publicly disclosed their pre-clinical research efforts.

Many of the companies against which we are competing or against which we may compete in the future, either alone or through collaborations, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and sales and marketing personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Furthermore, we also face competition more broadly across the oncology market for cost-effective and reimbursable cancer treatments. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates, if any are approved, may compete with these existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates may not be competitive with them. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. As a result, obtaining market acceptance of, and gaining significant share of the market for, any of our product candidates that we successfully introduce to the market may pose challenges. In addition, many companies are developing new oncology therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient to administer, are less expensive or with a more favorable labeling than our current or future product candidates. Our competitors also may obtain FDA, foreign regulatory authority, or other marketing or regulatory approval for their products more rapidly than any approval we may obtain for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the level of generic competition and the availability of reimbursement from government and other third-party payors.

***Even if we are able to commercialize any product candidates, the products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.***

The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product candidate in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues, if any, we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if such product candidates obtain marketing approval.

Our ability to commercialize any product candidates successfully also will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors, including government healthcare programs, private health insurers and other organizations. Third-party payors decide which medications they will pay for and establish reimbursement levels. In the United States, the principal decisions about reimbursement for new medicines are typically made by the CMS, which decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors often, but not always, follow CMS's decisions regarding coverage and reimbursement.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Coverage and reimbursement may not be available for any product that we commercialize and, even if these are available, the level of reimbursement may not be satisfactory to cover the costs of research, development, manufacture, sale and distribution. Reimbursement may affect the demand for, or the price of, any product candidate for which we obtain marketing approval. Obtaining and maintaining coverage and adequate reimbursement for our products may be difficult. We may be required to conduct expensive pharmacoeconomic studies to justify coverage and reimbursement or the level of reimbursement relative to other therapies. If coverage and adequate reimbursement are not available or reimbursement is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

Additionally, we may develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. We, or our collaborators, if any, will be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved. While we have not yet developed any companion diagnostic test for our product candidates, if we do, there is significant uncertainty regarding our ability to obtain coverage and adequate reimbursement for the same reasons applicable to our product candidates.

There may also be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, intellectual property, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs 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 drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies, but also have their own methods and approval process apart from Medicare determinations. Our inability to promptly obtain coverage and adequate reimbursement rates from third-party payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

***Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.***

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercialize any products that we may develop. If we cannot successfully defend ourselves against any claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- initiation of investigations by regulators;
- withdrawal of clinical trial participants;
- significant time and costs to defend the related litigation;



- diversion of management and scientific resources from our business operations;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Our current product liability insurance coverage for the United States and certain other jurisdictions may not be adequate to cover all liabilities that we may incur. We likely will need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. 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. A successful product liability claim or series of claims brought against us could decrease our cash and adversely affect our business and financial condition.

### **Risks Related to Employee Matters and Our Operations**

***Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel and manage our human capital.***

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the development and management expertise of Kris Vaddi, Ph.D., our founder and Chief Executive Officer, as well as the other principal members of our management, scientific and clinical team. We currently do not maintain key person insurance on these individuals. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time.

Our industry has experienced a high rate of turnover in recent years. Our ability to compete in the highly competitive pharmaceuticals industry depends upon our ability to attract, retain and motivate highly skilled and experienced personnel with scientific, clinical, regulatory, manufacturing and management skills and experience. We conduct our operations in the greater Delaware area, a region that is home to other pharmaceutical companies as well as many academic and research institutions. Additionally, companies are more willing to hire remote workers following the COVID-19 pandemic resulting in fierce competition for qualified personnel. We may not be able to attract or retain qualified personnel in the future due to the intense competition for a limited number of qualified personnel among pharmaceutical companies. Many of the other pharmaceutical companies against which we compete have greater financial and other resources, different risk profiles and a longer history in the industry than we do. Our competitors may provide higher compensation, more diverse opportunities and/or better opportunities for career advancement. Any or all of these competing factors may limit our ability to continue to attract and retain high quality personnel, which could negatively affect our ability to successfully develop and commercialize our product candidates and to grow our business and operations as currently contemplated.

***We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

As of December 31, 2023, we had 128 full-time employees. We expect significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, clinical operations, manufacturing, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, 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 and with developing sales, marketing and distribution infrastructure, 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.

Further, we currently rely, and for the foreseeable future will continue to rely, in substantial part on certain third-party contract organizations, advisors and consultants to provide certain services, including assuming substantial responsibilities for the conduct of our clinical trials and the manufacturing of any of our product candidates. We cannot assure you that the

services of such third-party contract organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by our vendors or consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of any of our product candidates or otherwise advance our business. We cannot assure you that we will be able to properly manage our existing vendors or consultants or find other competent outside vendors and consultants on economically reasonable terms, or at all.

If we are not able to effectively manage growth and expand our organization, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development and commercialization goals.

***Our employees, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.***

We are exposed to the risk of fraud or other misconduct by our employees, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential commercial partners. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (i) FDA regulations or those of comparable foreign regulatory authorities, including those laws that require the reporting of true, complete and accurate information, (ii) manufacturing standards, (iii) federal and state health and data privacy, security, fraud and abuse, government price reporting, transparency reporting requirements, and other healthcare laws and regulations in the United States and abroad, (iv) sexual harassment and other workplace misconduct laws, or (v) laws that require the true, complete and accurate reporting of financial information or data. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation.

We have adopted a code of conduct applicable to all of our employees, consultants, vendors and other potential commercial partners, as well as a disclosure program and other applicable policies and procedures, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from an alleged 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, including the imposition of significant civil and administrative penalties and damages, criminal fines and confinement, disgorgement, exclusion from participation in government funded healthcare programs, such as Medicare, Medicaid and other federal healthcare programs, suspension and debarment from government procurement and non-procurement programs, refusal of orders under existing government contracts, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

***Our internal information technology systems, or those of our third-party CROs, CMOs, or other vendors, contractors or consultants, may fail or suffer security breaches, cyber-attacks, loss or leakage of data and other disruptions, which could result in a material disruption of our development programs, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability or otherwise adversely affecting our business.***

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party CROs, CMOs, vendors, and other contractors and consultants who have access to our confidential information. Our internal information technology systems and infrastructure are also vulnerable to damage from natural disasters, terrorism, war, telecommunication and electrical failures. System failures or outages could compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting. Such failures could materially adversely affect our operating results and financial condition.

Despite the implementation of security measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third-party CROs, CMOs, vendors and other contractors and consultants (collectively, “Third Parties”) are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, accidents by our employees or third party service providers, natural disasters, terrorism, war and telecommunication and electrical failures. Our systems, and those of Third Parties, may also experience security breaches from inadvertent or intentional actions by our employees, or from cyber-attacks by malicious third parties including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. We may not be able to anticipate all types of security threats, nor may we be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies. If a disruption or security breach were to result in a loss of, or damage to, our data or applications, or those of our Third Parties, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of our product candidates could be delayed. Any breach, loss or compromise of clinical trial participant personal data may also subject us to civil damages and penalties, under HIPAA and other relevant state and federal privacy laws. The costs related to significant security breaches or disruptions could be material and exceed the limits of the cybersecurity insurance we maintain against such risks. If the information technology systems of our Third Parties become subject to disruptions or security breaches, we may have insufficient recourse against such third parties and we may have to expend significant resources to mitigate the impact of such an event, and to develop and implement protections to prevent future events of this nature from occurring. Any such incident that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business.

***Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business.***

We and any potential collaborators may be subject to federal, state and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws, state consumer privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy, data protection and security requirements under HIPAA, as amended by HITECH. Depending on the facts and circumstances, we could be subject to criminal penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

International data protection laws, including Regulation 2016/679, known as the General Data Protection Regulation, or GDPR, may also apply to health-related and other personal information obtained outside of the United States. The regulation imposes numerous new requirements for the collection, use and disclosure of personal information, including more stringent requirements relating to consent and the information that must be shared with data subjects about how their personal information is used, the obligation to notify regulators and affected individuals of personal data breaches, internal privacy governance obligations and obligations to honor expanded rights of individuals in relation to their personal information (e.g., the right to access, correct and delete their data). In addition, the GDPR includes restrictions on cross-border data transfer, which may require ongoing changes to our business operations, implementation of revised legal mechanisms, and other challenges. The GDPR features potential fines for noncompliant companies of up to the greater of €20 million or 4% of annual global revenue. The GDPR and other international data protection laws will increase our responsibility and liability in

relation to personal data that we process, and we may be required to put in place additional mechanisms to ensure compliance.

In addition, data protection requirements and risk are increasing in the United States. The state of California enacted the California Consumer Privacy Act, or CCPA, which creates new individual privacy rights for California consumers (as defined in the CCPA), including the rights to access, correction, and deletion and places increased privacy and security obligations on entities handling certain personal data of consumers or households. The CCPA requires covered companies to provide detailed disclosures to consumers about such companies' data collection, use and sharing practices, provide such consumers new ways to opt-out of certain sales or transfers of personal information, and provide consumers with additional causes of action. Following California's lead, other states have adopted similar comprehensive consumer privacy laws, all of which may impact our business activities and exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information. The CCPA and other state privacy laws provide for significant civil penalties for violations, and California now provides for a private right of action for data breaches that is expected to increase data breach litigation. These regulatory changes may increase our compliance costs and potential liability, particularly in the event of a data breach.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with U.S. and international data protection laws and regulations could result in government enforcement actions (which could include civil, criminal, and administrative penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time consuming to defend and could result in adverse publicity that could harm our business.

***We or the third parties upon whom we depend may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.***

Our company is located in Delaware. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemic, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize our facilities, or the manufacturing facilities of our third-party CMOs, may have a material and adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. For example, our operations are concentrated primarily on the east coast of the United States, and any adverse weather event or natural disaster, such as a hurricane or heavy snowstorm, could have a material adverse effect on a substantial portion of our operations. Extreme weather conditions or other natural disasters could further disrupt our operations and have a material and adverse effect on our business, financial condition, results of operations and prospects. In addition, the long-term effects of climate change on general economic conditions and the pharmaceutical industry in particular are unclear and may heighten or intensify existing risk of natural disasters. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our research facilities or the manufacturing facilities of our third-party CMOs, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities, or the manufacturing facilities of our third-party CMOs, are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption could have a material and adverse effect on our business, financial condition, results of operations and prospects.

***Disruptions at the FDA, the SEC and other government agencies caused by funding shortages or government shutdowns could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner, or otherwise prevent those agencies from performing normal business functions, which could negatively impact our business.***

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely is subject to the impacts of political events, which are inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which could adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA and the SEC to timely review and process our submissions, which could have a material adverse effect on our business.

***Changes in tax laws or regulations that are applied adversely to us may have a material adverse effect on our business, cash flow, financial condition or results of operations.***

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Cuts and Jobs Act, enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Cuts and Jobs Act may affect us, and certain aspects of the Tax Cuts and Jobs Act could be repealed or modified in future legislation. For example, the CARES Act modified certain provisions of the Tax Cuts and Jobs Act. In addition, it is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act, the CARES Act, or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Cuts and Jobs Act, the CARES Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

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

We have incurred substantial losses during our history and do not expect to become profitable in the near future, and we may never achieve profitability. Unused losses incurred in taxable years beginning on or prior to December 31, 2017, will carry forward to offset future taxable income, if any, until such unused losses expire. Under the Tax Cuts and Jobs Act, as modified by the CARES Act, unused U.S. federal net operating losses generated in tax years beginning after December 31, 2017 will not expire and may be carried forward indefinitely but the deductibility of such federal net operating losses (particularly those generated in taxable years beginning after December 31, 2020) in taxable years beginning after December 31, 2020 is limited to 80% of current year taxable income. It is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act or the CARES Act. In addition, both our current and our future unused losses and other tax attributes may be subject to limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code) if we undergo, or have undergone, an “ownership change,” generally defined as a greater than 50 percentage point change (by value) in our equity ownership by certain stockholders over a three-year period. We have not completed a Section 382 study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since our formation due to the complexity and cost associated with such a study and the fact that there may be additional ownership changes in the future. As a result, our net operating loss carryforwards generated in taxable years beginning on or before December 31, 2017, may expire prior to being used, and the deductibility of our net operating loss carryforwards generated in taxable years beginning after December 31, 2017 in taxable years beginning after December 31, 2020 may be limited, and, if we undergo an ownership change (or if we previously underwent such an ownership change), our ability to use all of our pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset our post-change income or taxes may be limited. Similar provisions of state tax law may also apply to limit our use of accumulated state tax attributes. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, even if we attain profitability, we may be unable to use all or a material portion of our net operating losses and other tax attributes, which could adversely affect our future cash flows.

***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, businesses or assets and out-licensing or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near term or long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations, systems and personnel of any acquired businesses with our operations, systems and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

***Our portfolio of investments or bank deposits may be subject to market, interest and credit risk that may reduce in value.***

The value of our investments may decline due to increases in interest rates, downgrades of the bonds and other securities included in our commercial money market account portfolio and instability in the global financial markets that reduces the liquidity of securities included in our portfolio. Furthermore, a possible recession, rising inflation, and the ongoing COVID-19 pandemic has and may continue to adversely affect the financial markets in some or all countries worldwide. Each of these events may cause us to record charges to reduce the carrying value of our investment portfolio or sell investments for less than our acquisition cost. Although we attempt to mitigate these risks through diversification of our investments and continuous monitoring of our portfolio's overall risk profile, the value of our investments may nevertheless decline.

### **Risks Related to Intellectual Property**

***If we are unable to obtain and maintain sufficient patent protection for our product candidates, or if the scope of the patent protection is not sufficiently broad, third parties, including our competitors, could develop and commercialize products similar or identical to ours, and our ability to commercialize our product candidates successfully may be adversely affected.***

Our success depends in large part on our ability to protect our proprietary technologies that we believe are important to our business, including pursuing, obtaining and maintaining patent protection in the United States and other countries intended to cover the compositions of matter of our product candidates, their methods of use, related technologies and other inventions that are important to our business. In addition to patent protection, we also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. If we do not adequately pursue, obtain, maintain, protect or enforce our intellectual property, third parties, including our 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 have currently filed patent applications in the United States related to our product candidates that we consider important to our business, including patent applications relating to compositions of matter covering our compounds, the processes for manufacturing such compounds and use of such compounds in therapies. We have also filed patent applications in foreign jurisdictions relating to our product candidates.

The patent application and approval process is expensive, time-consuming and complex. We may not be able to file, prosecute and maintain all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions. We also cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdictions. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, depending on the terms of any future license agreements to which we may become a party, we may not have the right to control the preparation, filing, and prosecution of patent applications, or to maintain the patents, covering technology licensed from third parties. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

Furthermore, the patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. The standards applied by the United States Patent and Trademark Office, or the USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. In addition, the determination of patent rights with respect to biological and pharmaceutical products commonly involves complex legal and factual questions, which have in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Thus, we cannot offer any assurances about which, if any, patents will issue, the breadth of any such patents, whether any issued patents will be found invalid and unenforceable or will be threatened by third parties or whether any issued patents will effectively prevent others from commercializing competing technologies and product candidates. We do not yet have issued patents on all of our product candidates.

Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until at least one patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent. However, prior to March 16, 2013, in the United States, the first to invent was entitled to the patent. Publications of discoveries in the scientific 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. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file or invent (prior to March 16, 2013) any patent application related to our product candidates. In addition, we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, collaborators, CROs, CMOs, hospitals, independent treatment centers, consultants, independent contractors, suppliers, advisors and other third parties; however, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Furthermore, if third parties have filed patent applications related to our product candidates or technology, we may not be able to obtain our own patent rights to those product candidates or technology.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. For example, we may be subject to a third-party pre-issuance submission of prior art to the USPTO or become involved in post-grant review procedures, oppositions, derivations, revocation, reexaminations, inter partes review or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse 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, or result in our inability to manufacture or commercialize products without infringing third-party rights. Moreover, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge priority of invention or other features of patentability. Such challenges may result in loss of exclusivity or in our patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products or limit the duration of the patent protection of our technology and products. Such challenges also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, our patents protecting such product candidates might expire before or shortly after such product 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, some of our patents and patent applications may in the future be co-owned with third parties. 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 may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Our pending and future patent applications may not result in patents being issued that protect our product candidates, in whole or in part, or which effectively prevent others from commercializing competitive products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by valid and enforceable patents. Our competitors and other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors and other third parties may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors or other third parties may seek to market generic versions or "follow-on" versions of any approved products by submitting abbreviated new drug applications, or ANDAs, or new drug applications under Section 505(b)(2) of the FDCA, respectively, to the FDA during which they may claim that patents owned by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Furthermore, future patents may be subject to a reservation of rights by one or more third parties. For example, to the extent the research resulting in future patent rights or technologies is funded in the future in part by the U.S. government, the government could have certain rights in any resulting patents and technology, including a non-exclusive license authorizing the government to use the invention or to have others use the invention on its behalf for non-commercial purposes. If the U.S. government then decides to exercise these rights, it is not required to engage us as its contractor in connection with doing so. These rights may also permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government may also exercise its march-in rights if it determines that action is necessary because we failed to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such government-funded inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of aforementioned proprietary rights could harm our competitive position, business, financial condition, results of operations, and prospects.

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

As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or the Leahy-Smith Act, signed into law in September 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S.



patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. For example, the Leahy-Smith Act allows third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, inter partes review, and derivation proceedings. In addition, the Leahy-Smith Act has transformed the U.S. patent system from a “first-to-invent” system to a “first-to-file” system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The first-to-file provisions, however, only became effective on March 16, 2013. It is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our or our future collaboration partners’ patent applications and the enforcement or defense of our or our future collaboration partners’ issued patents, all of which could harm our business, results of operations, financial condition and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

***We may become involved in lawsuits or administrative disputes to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.***

Competitors and other third parties may infringe, misappropriate or otherwise violate our patents, trademarks, copyrights, trade secrets or other intellectual property. To counter infringement, misappropriation or other violations, we may be required to file infringement, misappropriation or other violation claims, which can be expensive and time consuming and divert the time and attention of our management and business and scientific personnel. In addition, many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can.

Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their patents or their other intellectual property, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In patent litigation in the United States, counterclaims challenging the validity, enforceability or scope of asserted patents are commonplace. Similarly, third parties may initiate legal proceedings against us seeking a declaration that certain of our intellectual property is non-infringed, invalid or unenforceable. The outcome of any such proceeding is generally unpredictable.

In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent’s claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. If a defendant were to prevail on a legal assertion of invalidity or unenforceability of our patents covering one of our product candidates, we could lose at least a part, and perhaps all, of the patent protection covering such a product candidate. Competing drugs may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit, alleging our infringement of a competitor’s patents, we could be prevented from marketing our drugs in one or more foreign countries. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. 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 litigation. There could also 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 material adverse effect on the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Furthermore, third parties may also raise invalidity or unenforceability claims before administrative bodies in the United States or foreign authorities, even outside the context of litigation. Such mechanisms include re-examination, inter partes review, post-grant review, interference proceedings, derivation proceedings and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation, cancellation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or written description. Grounds for an unenforceability assertion could be an allegation that someone connected with the prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution of the patent. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we, our licensors, our patent counsel and the patent examiner were unaware during prosecution. Moreover, it is possible that prior art may exist that we are aware of but do not believe is relevant to our current or future patents, but that could nevertheless be determined to render our patents invalid. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates. Any such loss of patent protection could have a material adverse impact on our business, financial condition, results of operations and prospects.

***We may not be able to effectively protect or enforce our intellectual property and proprietary rights throughout the world.***

Filing, prosecuting and defending patents with respect to our product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. The requirements for patentability may differ in certain countries, particularly in developing countries. In addition, any future intellectual property license agreements may not always include worldwide rights. Consequently, competitors and other third parties 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 may obtain patent protection, but where patent enforcement is not as strong as that in the United States and where our ability to enforce our patents to stop infringing activities may be inadequate. These products may compete with our products in such territories and in jurisdictions where we do not have any patent rights or where any future patent claims or other intellectual property or proprietary rights may not be effective or sufficient to prevent them from competing with us, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Moreover, our ability to protect and enforce our intellectual property and proprietary rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, the laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property and proprietary rights in certain foreign jurisdictions. The legal systems of some countries, including, for example, India, China and other developing countries, do not view favorably the enforcement of patents and other intellectual property or proprietary rights, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement, misappropriation or other violation of our patents or other intellectual property or proprietary rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe. In addition, many countries 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 are 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, financial condition, results of operations, and prospects may be adversely affected. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business, could put our patents, trademarks or other intellectual property and proprietary rights at risk of being invalidated or interpreted narrowly, could put 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. Furthermore, while we intend to protect our intellectual property and proprietary rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property and proprietary rights in such countries may be inadequate.

Further, the complexity and uncertainty of European patent laws have increased in recent years. In Europe, a new unitary patent system was introduced in early 2023, which could significantly impact European patents, including those granted before the introduction of such a system. Under the unitary patent system, European applications have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court, or the UPC. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation. Patents granted before the implementation of the UPC have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC could be potentially vulnerable to a single UPC-based revocation challenge that, if successful, could invalidate the patent in all countries who are signatories to the UPC. We cannot predict with certainty the long-term effects of any potential changes.

***If we are sued for infringing, misappropriating or otherwise violating intellectual property or proprietary rights of third parties, such litigation or disputes could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.***

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and other proprietary rights of third parties. If any third-party patents, patent applications or other proprietary rights are found to cover our product candidates or any related companion diagnostics or their compositions, methods of use or manufacturing, we may be required to pay damages, which could be substantial, and we would not be free to manufacture or market our product candidates or to do so without obtaining a license, which may not be available on commercially reasonable terms, or at all.

We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property or proprietary rights with respect to our product candidates and technologies we use in our business. Our competitors or other third parties may assert infringement claims against us, alleging that our product candidates are covered by their patents. We cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our product candidates. If a patent holder believes our product candidate infringes its patent rights, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property or proprietary rights with respect to our product candidates, including interference proceedings before the USPTO. Third parties may assert infringement, misappropriation or other claims against us based on existing or future intellectual property or proprietary rights. The outcome of intellectual property litigation and other disputes is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of using or manufacturing products. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods of use, manufacturing or other applicable activities either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be successful in doing so. However, proving invalidity or unenforceability is difficult. For example, in the United States, proving invalidity requires a showing of

clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, or enforceability. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and business and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property or proprietary rights and we are unsuccessful in demonstrating that such intellectual property or proprietary rights are invalid or unenforceable, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby giving our competitors and other third parties access to the same technologies licensed to us. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed such third-party patent rights. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

***We may be subject to claims by third parties asserting that our employees or consultants or we have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.***

Some of our employees and consultants are currently or have been previously employed at universities or at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. These employees and consultants may have executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such other current or previous employment. Although we try to ensure that our employees and consultants 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 these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of third parties. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property or personnel or sustain damages. Such intellectual property could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management. Any of the foregoing would have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, while it is our policy to require our employees, consultants and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. In addition, such agreements may not be self-executing such that the intellectual property subject to such agreements may not be assigned to us without additional assignments being executed, and we may fail to obtain such assignments. In addition, such agreements may be breached. In addition, we have multiple sponsored research agreements relating to our lead product candidates with various academic institutions. Some of these academic institutions may not have intellectual property assignments or similar agreements with their employees and consultants, which may result in claims by or against us related to ownership of any intellectual property. Accordingly, we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

***Rights to improvements to our product candidates may be held by third parties.***

In the course of testing our product candidates, we have entered into agreements with third parties to conduct clinical testing, which provide that improvements to our product candidates may be owned solely by a party or jointly between the parties. If we determine that rights to such improvements owned solely by a third party are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to use the improvements and continue developing, manufacturing or marketing the product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby giving our competitors and other third parties access to the same technologies licensed to us. Failure to obtain a license on commercially reasonable terms or at all, or to obtain an exclusive license, could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. If we determine that rights to improvements jointly owned between us and a third party are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain an exclusive license from such third party. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such improvements, 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 may need the cooperation of any such co-owners of our intellectual property in order to enforce such intellectual property against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

***The term of our patents may be inadequate to protect our competitive position on our products.***

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. Depending upon the timing, duration and other factors relating to any FDA marketing approval we receive for any of our 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. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Hatch-Waxman Amendments permit a patent term extension of up to five years beyond the normal expiration of the patent, limited to the approved indication (or any additional indications approved during the period of extension), as compensation for patent term lost to the regulatory review process during which the sponsor was unable to commercially market its new product. 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 applicable to an approved drug is eligible for the extension and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended, and the application for the extension must be submitted prior to the expiration of the patent. However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available for our patents, may refuse to grant extensions to our patents, or may grant more limited extensions than we request. 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. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors and other third parties may be able to obtain approval of competing products following our patent expiration and take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. Any of the foregoing would have a material adverse effect on our business, financial condition, results of operations and prospects.

***Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment and other requirements imposed by governmental patent offices, and our patent protection could be reduced or eliminated for noncompliance with these requirements.***

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on any issued patent are due to be paid to the USPTO and patent offices in foreign countries in several stages over the lifetime of the patent. The USPTO and patent offices in foreign countries require compliance with a number of procedural, documentary, fee payment and other requirements during the patent application process. In the future, we may rely on licensing partners to pay these fees due to U.S. and non-U.S. patent agencies and to comply with these other requirements with respect to any future licensed patents and patent applications. While an inadvertent lapse can 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 a patent or patent rights in the relevant jurisdiction. Non-compliance 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 and other third parties might be able to enter the market with similar or identical products of technology, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

***If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.***

We rely on proprietary know-how and trade secret protection and confidentiality agreements to protect proprietary know-how or trade secrets that are not patentable or that we elect not to patent. We seek to protect our trade secrets and proprietary know-how in part by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, such as our employees, consultants, independent contractors, advisors, CMOs, CROs, hospitals, independent treatment centers, suppliers, collaborators and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary know-how. Additionally, our confidentiality agreements and other contractual protections may not be adequate to protect our intellectual property from unauthorized disclosure, third-party infringement or misappropriation. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts in the United States and certain foreign jurisdictions are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our business, financial condition, results of operations and prospects our business and competitive position could be materially harmed.

***Intellectual property rights do not necessarily address all potential threats.***

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products similar to any product candidates we may develop or utilize similarly related technologies that are not covered by the claims of the patents that we may license or may own in the future;
- we, or any future license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or any future license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating any of our owned or licensed intellectual property rights;
- it is possible that our pending patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and

- we may choose not to file a patent in order to maintain certain trade secrets or know how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

## **Risks Related to Our Common Stock**

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

As of December 31, 2023, our executive officers, directors, beneficial owners of 5% or more of our capital stock and their respective affiliates beneficially owned approximately 45% of our common stock and securities convertible into shares of our common stock. The voting power of this group may increase to the extent they convert shares of non-voting common stock or pre-funded warrants that they hold into shares of our common stock.

This concentration of control creates a number of risks. This group of stockholders has the ability to control us through this ownership position and are able to determine all matters requiring stockholder approval. For example, these stockholders are able to control elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction, and other stockholders may find it difficult to replace members of management should they disagree with the manner in which the Company is operated. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

***An active and liquid trading market for our common stock may never be sustained. As a result, you may not be able to resell your shares of common stock at or above the purchase price.***

An active trading market for our common stock may never be sustained. The market value of our common stock may decrease from the purchase price. As a result of these and other factors, you may be unable to resell your shares of our common stock at or above the purchase price. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair market value of your shares. Furthermore, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic collaborations or acquire companies or products by using our shares of common stock as consideration.

***Our quarterly operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.***

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expense related to the planned and ongoing development of our product candidates or future development programs, including scale-up CMC expenses;
- results of clinical trials, or the addition or termination of future preclinical or clinical trials or funding support by us, or future collaborators or licensing partners;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under existing or future arrangements or the termination or modification of any such existing or future arrangements;
- any intellectual property infringement lawsuit or opposition, interference or cancellation proceeding in which we may become involved;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;

- if any of our product candidates receives regulatory approval, the terms of such approval and market acceptance and demand for such product candidates;
- regulatory developments affecting our product candidates or those of our competitors; and
- changes in political, economic and general macroeconomic conditions, including but not limited to the ongoing conflict in Ukraine, supply chain disruptions, rising interest rates, rising inflation rates, a potential recession or the ongoing COVID-19 pandemic.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our common stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

***The market price of our common stock has been, and is likely to be, highly volatile, which could result in substantial losses for purchasers of our common stock.***

From January 1, 2023 to December 31, 2023, the closing price of common stock on the Nasdaq Global Select Market ranged from \$1.69 to \$8.12 per share. The market price of our common stock is likely to continue to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid. The market price for our common stock may be influenced by many factors, including the other risks described in this section of this Annual Report on Form 10-K and the following:

- enrollment or results of clinical trials of our product candidates, or those of our competitors or our future collaborators, or changes in the development status of our product candidates;
- the failure of any product candidates;
- regulatory or legal developments in the United States and other countries, especially changes in laws or regulations applicable to our product candidates;
- the success of competitive products or technologies;
- introductions and announcements of new products by us, our future commercialization partners, or our competitors, and the timing of these introductions or announcements;
- actions taken by regulatory agencies with respect to our products, clinical studies, manufacturing process or sales and marketing terms;
- actual or anticipated variations in our financial results or those of companies that are perceived to be similar to us;
- the success of our efforts to acquire or in-license additional technologies, products or product candidates;
- developments concerning any future collaborations, including but not limited to those with development and commercialization partners;
- market conditions in the pharmaceutical and biotechnology sectors;
- developments or disputes concerning patents or other proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our product candidates and products;
- our ability or inability to raise additional capital and the terms on which we raise it;
- the recruitment or departure of key personnel;
- changes in the structure of healthcare payment systems;
- announcement and expectation of additional financing efforts;
- sales or purchases of our common stock by us, insiders or our stockholders;
- general economic, industry and market conditions, or other events or factors, many of which are beyond our control, including but not limited to a potential recession, rising interest rates, rising inflation, and the recent COVID-19 pandemic.



In addition, the stock market in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme price and volume fluctuations that have been often unrelated or disproportionate to the operating performance of the issuer. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this “Risk Factors” section, could have a dramatic and adverse impact on the market price of our common stock.

***The dual class structure of our common stock may limit your ability to influence corporate matters and may limit your visibility with respect to certain transactions.***

The dual class structure of our common stock may limit your ability to influence corporate matters. Holders of our common stock are entitled to one vote per share, while holders of our non-voting common stock are not entitled to any votes. Nonetheless, each share of our non-voting common stock, as well as our pre-funded warrants, may be converted at any time into one share of our common stock at the option of its holder by providing written notice to us, subject to the limitations provided for in our restated certificate of incorporation. Consequently, if holders of our non-voting common stock and pre-funded warrants exercise their option to make this conversion, this will have the effect of increasing the relative voting power of those prior holders of our non-voting common stock, and correspondingly decreasing the voting power of the holders of our common stock, which may limit your ability to influence corporate matters. For example, on February 9, 2024, the common stock will have 100% of the voting power, but if the holders of non-voting common stock or pre-funded warrants were to convert all of their shares or pre-funded warrants into common stock, the prior common stock would have 55.5% of the voting power, and the former non-voting common stock and holders of pre-funded warrants would represent 44.5 of the voting power. Additionally, stockholders who hold, in the aggregate, more than 10% of our common stock, non-voting common stock and pre-funded warrants, but 10% or less of our common stock, and are not otherwise an insider of the company, may not be required to report changes in their ownership due to transactions in our non-voting common stock pursuant to Section 16(a) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and may not be subject to the short-swing profit provisions of Section 16(b) of the Exchange Act.

***We are an “emerging growth company” and a “smaller reporting company” and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies or smaller reporting companies will make our common stock less attractive to investors.***

We are an “emerging growth company” as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including (i) not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, or the Sarbanes-Oxley Act, (ii) reduced disclosure obligations regarding executive compensation in this Annual Report on Form 10-K as well as our periodic reports and proxy statements and (iii) exemptions from the requirements of holding nonbinding advisory stockholder votes on executive compensation and stockholder approval of any golden parachute payments not approved previously. In addition, as an emerging growth company, we are only required to provide two years of audited financial statements in this Annual Report on Form 10-K.

We could be an emerging growth company until December 31, 2025, although circumstances could cause us to lose that status earlier, including if we are deemed to be a “large accelerated filer,” which occurs when the market value of our common stock that is held by non-affiliates equals or exceeds \$700 million as of the prior June 30, or if we have total annual gross revenue of \$1.235 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31, or if we issue more than \$1.0 billion in non-convertible debt during any three-year period before that time, in which case we would no longer be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a “smaller reporting company,” which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, if our revenues remain less than \$100.0 million, and reduced disclosure obligations regarding executive compensation in this Annual Report on Form 10-K as well as our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may 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 share price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to take advantage of the benefits of this extended transition period. Our financial statements may therefore not be comparable to those of companies that comply with such new or revised accounting standards. Until the date that we are no longer an “emerging growth company” or affirmatively and irrevocably opt out of the exemption provided by Section 7(a)(2)(B) of the Securities Act, upon issuance of a new or revised accounting standard that applies to our financial statements and that has a different effective date for public and private companies, we will disclose the date on which adoption is required for non-emerging growth companies and the date on which we will adopt the recently issued accounting standard.

We are also a “smaller reporting company,” meaning that the market value of our stock held by non-affiliates is less than \$700.0 million as of the prior June 30 and our annual revenue is less than \$100.0 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 stock held by non-affiliates is less than \$250.0 million or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than \$700.0 million as of the prior June 30. 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. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

***Anti-takeover provisions in our charter documents and under Delaware law could prevent or delay an acquisition of us, which may be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.***

Our restated certificate of incorporation and our restated bylaws contain provisions that could delay or prevent a change in control of our company. These provisions could also make it difficult for stockholders to elect directors who are not nominated by current members of our board of directors or take other corporate actions, including effecting changes in our management. These provisions:

- establish a classified board of directors so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed “for cause” and only with the approval of two-thirds of our stockholders;
- require super-majority voting to amend some provisions in our restated certificate of incorporation and restated bylaws;
- authorize the issuance of “blank check” preferred stock that our board could use to implement a stockholder rights plan;
- eliminate the ability of our stockholders to call special meetings of stockholders;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- prohibit cumulative voting; and
- establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings.

In addition, Section 203 of the Delaware General Corporation Law, or DGCL, may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15% or more of our common stock.

***The exclusive forum provision in our organizational documents may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims.***

Our restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our restated certificate of incorporation, or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision does not apply to suits brought to enforce a duty or liability created by the Exchange Act. It could apply, however, to a suit that falls within one or more of the categories enumerated in the exclusive forum provision.

This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations and financial condition.

Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all claims brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. Our restated bylaws provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or a Federal Forum Provision. Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court.

Section 27 of the Exchange Act creates exclusive federal jurisdiction over all claims brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. In addition, neither the exclusive forum provision nor the Federal Forum Provision applies to suits brought to enforce any duty or liability created by the Exchange Act. Accordingly, actions by our stockholders to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder must be brought in federal court.

Our stockholders will not be deemed to have waived our compliance with the federal securities laws and the regulations promulgated thereunder.

Any person or entity purchasing or otherwise acquiring or holding any interest in any of our securities shall be deemed to have notice of and consented to our exclusive forum provisions, including the Federal Forum Provision. These provisions may limit a stockholders' ability to bring a claim in a judicial forum of their choosing for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees.

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

As a public company, and particularly after we are no longer an emerging growth company, we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market 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, we expect these rules and regulations to substantially increase our legal and financial compliance costs and to make some activities more time consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain sufficient coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. The increased costs may require us to reduce costs in other areas of our business or increase the prices of our products once commercialized. Moreover, 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.

***Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.***

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

## **General Risk Factors**

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

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If no or few securities or industry analysts commence coverage of us, the trading price for our common stock could be impacted negatively. In the event we obtain securities or industry analyst coverage, if any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our preclinical studies and clinical trials and operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of such analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause a decline in our stock price or trading volume.

***If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.***

We are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act and the rules and the listing requirements of the Nasdaq Global Select Market. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting.

We perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting in our Annual Report on Form 10-K filing for that year, as required by Section 404(a) of the Sarbanes-Oxley Act. This requires that we incur substantial additional professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts.

Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our stock could decline and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the SEC, or other regulatory authorities.

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

The market price of our common stock may be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

## **Item 1B. Unresolved Staff Comments.**

None.

## **Item 1C. Cybersecurity**

### **Risk Management and Strategy**

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. These systems are connected to and/or accessed from the Internet and, as a result, are susceptible to cyber-attacks. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. A material cyber-attack on our systems, or any other third-party partners or vendors and their key operating systems, may interrupt our ability to operate our business, damage our reputation, or result in monetary damages.

Prelude has established an Information Security Policy ("IS Policy") in order to establish the high-level direction for properly managing the use, privacy, security, retention, and disposal of Prelude's information and its assets. The IS Policy was prepared using relevant guidance issued and technology standards that are used across various industries. The IS policy applies to all entities who are using Prelude's equipment and resources, including but not limited to: employees, contractors, temporary workers, any third parties with access to the Prelude's resources, and cloud IT providers. Prelude's Head of Information Technology ("IT") also serves as our Information Security Officer and is primarily responsible for implementing and overseeing the IS Policy and identifying, measuring, monitoring, and reporting on key enterprise-wide risks, including cybersecurity risks.

Prelude has also established an Incident Response Policy which includes reporting thresholds and follows standardized identification and authentication practices. If an incident is identified, it is documented by Prelude's Head of IT, who in turn, will report the incident to necessary management members.

### **Board Governance and Management**

Prelude's Information Security Officer provides updates on information technology risks, controls and procedure, including Prelude's plans to mitigate cybersecurity risks and respond to data breaches to Prelude's executive leadership team. Our Information Security Officer has over 20 years of experience in information security and possesses the requisite education, skills, experience, and industry certifications expected of an individual assigned to these duties. The Chief Financial Officer and the Chief Legal Officer report to the Chair of the Audit Committee prompt and timely information regarding any significant cybersecurity incident. The significant incident will be reported to the remaining Audit Committee members, as well as ongoing updates regarding any such incident until it has been addressed. Such incidents, as warranted, will be reviewed by the Board of Directors.

The Board of Directors has delegated responsibility for cybersecurity risk oversight to the Audit Committee, which is responsible for (i) regularly reviewing with management significant cybersecurity, privacy, and IT risks or exposures, and the Company's policies and processes with respect to risk assessment and risk management of the same; (ii) regularly reviewing with management an assessment of the steps management has taken to monitor and control such risks; and (iii) regularly reporting to the full Board of Directors on such matters. The Chair of the Audit Committee has expertise in risk management which includes IT and cybersecurity.

Notwithstanding the approach we take to cybersecurity, we may not be successful in preventing or mitigating a cybersecurity incident that could have a material adverse effect on us. See Item 1A. "Risk Factors" for a discussion of cybersecurity risks.

## **Item 2. Properties.**

In December 2023, we relocated our principal executive offices to Chestnut Run Plaza in Wilmington, Delaware. The facility has approximately 81,000 square feet of office and laboratory space that we use for administrative, research and development and other activities. The Chestnut Run Lease has an initial term of 162 months with three five-year extension options and certain expansion rights.

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 be involved in legal proceedings arising in the ordinary course of our business. In addition, we may receive letters alleging infringement of patents or other intellectual property rights. We are not presently a party to any legal proceedings that, in the opinion of management, would have a material adverse effect on our business, operating results, cash flows or financial conditions should such litigation be resolved unfavorably. Regardless of outcome, litigation can have an adverse impact on us due to defense and settlement costs, diversion of management resources, negative publicity and reputational harm, and other factors.

**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 for Common Stock**

Our common stock has been listed on The Nasdaq Global Market under the symbol “PRLD” since September 25, 2020. Prior to that there was no public trading market for our common stock.

#### **Holders of Record**

As of February 9, 2024, there were approximately 17 stockholders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

#### **Dividend Policy**

We currently intend to retain future earnings, if any, for use in operation of our business and to fund future growth. We have never declared or paid any cash dividends on our capital stock and do not anticipate paying any cash dividends in the foreseeable future. Payment of cash dividends, if any, in the future will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

#### **Unregistered Sales of Equity Securities**

During the year ended December 31, 2023, we did not issue or sell any unregistered securities not previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

#### **Purchases of Equity Securities by the Issuer and Affiliated Purchasers**

None.

### **Item 6. [Reserved]**

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

*You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and the related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis contains forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described below.*

### Overview

Prelude is a clinical-stage fully integrated oncology company built on a foundation of drug discovery excellence to deliver novel precision cancer medicines to underserved patients. By leveraging our core competencies in cancer biology and medicinal chemistry, combined with our clinical development capabilities, we have built an efficient, fully-integrated drug discovery engine and the development expertise necessary to identify compelling biological targets and create new chemical entities, or NCEs, that we advance into clinical trials. We believe our approach could result in better targeted cancer therapies. Our discovery excellence has been validated by our steady progress in creating a wholly-owned, internally developed pipeline. We also began work with our partner AbCellera on an early-stage discovery program involving potent degraders as payloads for novel antibodies targeting tumor specific antigens. Since our inception in 2016, we have received clearance from the U.S. Food and Drug Administration, or the FDA, for multiple investigational new drug applications, or INDs, and successfully advanced several programs into clinical trials. In addition, we have other differentiated proprietary programs in various stages of preclinical development.

By focusing on developing molecules using broad mechanisms that have multiple links to oncogenic driver pathways in select patients, we have developed a diverse pipeline consisting of multiple distinct programs including kinases, targeted protein degraders, and precision antibody drug conjugates. Our pipeline is designed to serve patients with high unmet medical need, where there are limited or no treatment options. We believe we can best address these diseases by developing therapies that target primary and secondary resistance mechanisms.

We have several drug candidates in clinical development and our objective is to generate proof-of-concept clinical data to guide our future regulatory pathways to approval. Our SMARCA2 molecule is a unique, first-in-class protein degrader, targeting specific patient populations. Our CDK9 inhibitor is selective and potent, with a potentially superior safety profile over first-generation CDK9 inhibitors. Our next generation CDK4/6 inhibitor is specifically designed to be brain and tissue penetrant.

Our novel, first-in-class SMARCA2 degrader compounds and our potent, highly selective and potentially best-in-class CDK9 inhibitor represent our best opportunities for demonstrating clinical proof-of-concept in 2024 and advancing into potential Phase 2/3 registration studies. In 2023 we also announced a global partnership with AbCellera Biologics Incorporated ("AbCellera") that will allow us to combine our small molecules and degraders expertise with their antibody expertise to develop precision antibody drug conjugates. We also intend to explore continued clinical development with external partners for our CDK4/6.

PRT3789 is a first-in-class, highly selective degrader of SMARCA2 protein, which along with SMARCA4 controls gene regulation through chromatin remodeling. Cancer cells with SMARCA4 mutations are dependent on SMARCA2 for their growth and survival and selectively degrading SMARCA2 induces cell death in cancer cells while sparing normal cells in preclinical models. PRT3789 has been shown to be efficacious and well tolerated in multiple preclinical models of SMARCA4 deleted/mutated cancers as monotherapy and in combination with standards of care therapies. We believe a selective SMARCA2 degrader has the potential to be of benefit in up to 10% of Non-Small Cell Lung cancer, or NSCLC, patients in the United States including many other tumor types with the SMARCA4 mutation.

Patients with SMARCA4 mutations or deletions have poor clinical outcomes and limited treatment options. Therefore, mutated or deleted SMARCA4 cancers provide a potential biomarker to select those patients most likely to respond to treatment with a highly selective SMARCA2 degrader.

PRT3789 is currently in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. To date PRT3789 has completed the fifth dose escalation cohort and demonstrated selective, potent and dose dependent degradation of SMARCA2 with an acceptable safety profile. Based on PK/PD and safety data to date, the Company expects to conclude monotherapy dose escalation in the middle of 2024 and identify recommended phase 2 doses. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations has been initiated. Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in



combination with docetaxel, evaluate efficacy, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into a registrational clinical trial. We expect to present initial data in the second half of 2024 from patients currently enrolled in the Phase 1 trial.

Our discovery team has identified a series of highly selective and orally bioavailable SMARCA2 degraders. The lead oral molecule, PRT7732, is currently in IND enabling studies and on track to enter Phase 1 clinical development in the second half of 2024. PRT7732 is structurally distinct from PRT3789 and in addition, may provide clinically meaningful differences, more patient-friendly dosing and may have utility in earlier lines of therapy.

As one of our first precision ADC programs Prelude and our partner AbCellera began work on an early-stage discovery program involving potent degraders of the SMARCA family of proteins as payloads for novel antibodies targeting tumor specific antigens. Given the potent anti-tumor activity of these molecules in pre-clinical models of cancers beyond those targeted by our SMARCA2 selective degraders, we believe that these precision ADCs have the potential to extend the therapeutic utility of this class. The partnership includes up to five precision ADC targets. Under the terms of the agreement, Prelude and AbCellera will jointly discover, develop, and commercialize products emerging from the collaboration. AbCellera will lead manufacturing activities and Prelude will lead clinical development and global commercialization, subject to AbCellera's option to co-promote any resulting commercial products in the United States.

Our CDK9 candidate, PRT2527, is designed to be a potent and selective CDK9 inhibitor. We believe PRT2527 has the potential to avoid off-target toxicities, achieve substantial clinical activity and to become the best-in-class CDK9 inhibitor for hematologic malignancies.

In preclinical studies, PRT2527 was shown to reduce MCL1 and MYC protein levels and was highly active in preclinical models at well-tolerated doses. Our preclinical studies suggest that PRT2527 demonstrates high kinase selectivity and potency, providing opportunity for a wider therapeutic index compared to less selective CDK9 inhibitors, allowing for rapid development in combinations.

Preclinical data demonstrated that treatment with PRT2527 depleted oncogenic drivers with short half-lives, such as MYC and MCL1, and effectively induced apoptosis. PRT2527 treatment demonstrated robust efficacy in both hematological malignancies and solid tumor models with MYC dysregulation. Dose dependent increases in exposure and target engagement were observed as evidenced by MYC and MCL1 depletion to levels associated with tumor regression in preclinical models.

PRT2527 has completed a Phase 1 multi-dose escalation study (NCT05159518) in patients with solid tumors. In this study, PRT2527 was shown to achieve high levels of target inhibition and the potential to be better tolerated than existing CDK9 inhibitors, specifically, managing neutropenia and an absence of meaningful gastrointestinal events or hepatotoxicity.

The observed dose-dependent downregulation of MYC and MCL1 mRNA expression, CDK9 transcriptional targets, was consistent with the degree of target engagement required for preclinical efficacy. As predicted by the preclinical models, 12 mg/m<sup>2</sup> QW dosing showed optimal target inhibition and has been selected as the optimal dose. The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530). In this study, PRT2527 is advancing in monotherapy hematological indications, such as B-cell malignancies and acute myeloid leukemia (AML), and it has initiated the combination with zanubrutinib in B-cell malignancies. We expect to complete the monotherapy dose escalation in B-cell malignancies in the middle of 2024. A second cohort of patients with AML is expected to initiate in the first half of 2024 in monotherapy.

Our MCL1 candidate, PRT1419, was designed to be a potent and selective inhibitor of the anti-apoptotic protein, MCL1. We concluded Phase 1 development of PRT1419 and established a confirmation dose in hematological malignancies. Based on the potential to address the intended patient population with the CDK9 inhibitor which potently inhibits MCL-1, we decided to prioritize our CDK9 inhibitor, PRT2527, and to discontinue development of PRT1419.

PRT3645 is a brain and tissue penetrant molecule that potently targets CDK4/6 with a biased selectivity for CDK4. A Phase 1 multi-dose escalation clinical trial of PRT3645 is underway with the objective of establishing a biologically active dose confirmation. At the 2023 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, we presented data, showing that treatment with PRT3645 was associated with a substantial decrease in pRb and Ki67 expression, indicating a high level of target engagement at the doses evaluated. Also, PRT3645 was generally well tolerated in the initial three dose cohorts of patients with no clinically meaningful gastrointestinal, hematologic or neurological events reported to date, leveraging its enhanced selectivity profile. We intend to complete the dose escalation

portion of the Phase 1 clinical trial of PRT3645 this year and following its completion, to explore continued clinical development with external partners.

We were incorporated in February 2016 under the laws of the State of Delaware. Since inception, we have devoted substantially all of our resources to developing product and technology rights, conducting research and development, organizing and staffing our company, business planning and raising capital. We have incurred recurring losses, the majority of which are attributable to research and development activities, and negative cash flows from operations. We have funded our operations primarily through the sale of convertible preferred stock and common stock. Our net loss was \$121.8 million and \$115.4 million for the years ended December 31, 2023 and 2022, respectively. As of December 31, 2023, we had an accumulated deficit of \$456.4 million. Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures, and to a lesser extent, general and administrative expenditures. 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 current or future product candidates. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we advance our product candidates through all stages of development and clinical trials and, ultimately, seek regulatory approval. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical trials and our expenditures on other research and development activities.

We will need to raise substantial additional capital to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we plan to finance our operations through the sale of equity, debt financings or other capital sources, which may include collaborations with other companies or other strategic transactions. There are no assurances that we will be successful in obtaining an adequate level of financing as and when needed to finance our operations on terms acceptable to us or at all. Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. If we are unable to secure adequate additional funding, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more product candidates or delay our pursuit of potential in-licenses or acquisitions.

As of December 31, 2023, we had \$232.9 million in cash, cash equivalents, and marketable securities. We expect our existing cash, cash equivalents and marketable securities will enable us to fund our operating expense and capital expenditures into 2026.

## **Components of Results of Operations**

### ***Revenue***

To date, we have not recognized any revenue from any sources, including from product sales, and we do not expect to generate any revenue from the sale of products in the foreseeable future. If our development efforts for our product candidates are successful and result in regulatory approval, or license agreements with third parties, we may generate revenue in the future from product sales. However, there can be no assurance as to when we will generate such revenue, if at all.

### ***Operating Expenses***

#### ***Research and Development Expenses***

Research and development expenses consist primarily of costs incurred in connection with the discovery and development of our product candidates. We expense research and development costs as incurred, including:

- expenses incurred to conduct the necessary discovery-stage laboratory work, preclinical studies and clinical trials required to obtain regulatory approval;
- personnel expenses, including salaries, benefits and stock-based compensation expense for our employees engaged in research and development functions;

- costs of funding research performed by third parties, including pursuant to agreements with clinical research organizations, or CROs, that conduct our clinical trials, as well as investigative sites, consultants and CROs that conduct our preclinical and nonclinical studies;
- expenses incurred under agreements with contract manufacturing organizations, or CMOs, including manufacturing scale-up expenses and the cost of acquiring and manufacturing preclinical study and clinical trial materials;
- fees paid to consultants who assist with research and development activities;
- expenses related to regulatory activities, including filing fees paid to regulatory agencies; and
- allocated expenses for facility costs, including rent, utilities, depreciation and maintenance.

We track outsourced development costs and other external research and development costs to specific product candidates on a program-by-program basis, fees paid to CROs, CMOs and research laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. However, we do not track our internal research and development expenses on a program-by-program basis as they primarily relate to compensation, early research and other costs which are deployed across multiple projects under development.

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 our research and development expenses to increase significantly over the next several years as we increase personnel costs, including stock-based compensation, conduct our clinical trials, including later-stage clinical trials, for current and future product candidates and prepare regulatory filings for our product candidates.

#### *General and Administrative Expenses*

General and administrative expenses consist primarily of personnel expenses, including salaries, benefits and stock-based compensation expense, for employees and consultants in executive, finance and accounting, legal, operations support, information technology and human resource functions. General and administrative expense also includes corporate facility costs not otherwise included in research and development expense, including rent, utilities, depreciation and maintenance, as well as legal fees related to intellectual property and corporate matters and fees for accounting and consulting services.

We expect that our general and administrative expense will increase in the future to support our continued research and development activities, potential commercialization efforts and increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, legal support and accountants, among other expenses. Additionally, we anticipate increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with the requirements of Nasdaq and the Securities and Exchange Commission, or SEC, insurance and investor relations costs. If any of our current or future product candidates obtains U.S. regulatory approval, we expect that we would incur significantly increased expenses associated with building a sales and marketing team.

#### *Other Income, Net*

Other income, net consists primarily of interest earned on our cash equivalents and marketable securities and grant income received from the State of Delaware. We anticipate re-applying for the grant from the State of Delaware from time to time as long as we maintain qualifying headcount levels in the State of Delaware. We expect our interest income, net to increase due to our investment of cash received from the sale of common stock.

#### *Income Taxes*

Since our inception, we have not recorded any income tax benefits for the net operating losses, or NOLs, we have incurred or for our research and development tax credits, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our NOLs and tax credits will not be realized.

## Results of Operations

### Comparison of the Years Ended December 31, 2023 and 2022

The following table sets forth our results of operations for the years ended December 31, 2023 and 2022.

(in thousands)	Year ended December 31,		Change
	2023	2022	
Operating expenses:			
Research and development.....	\$ 103,393	\$ 92,889	\$ 10,504
General and administrative.....	28,884	30,651	(1,767)
Total operating expenses.....	132,277	123,540	8,737
Loss from operations.....	(132,277)	(123,540)	(8,737)
Other income, net.....	10,445	8,102	2,343
Net loss.....	<u>\$ (121,832)</u>	<u>\$ (115,438)</u>	<u>\$ (6,394)</u>

#### Research and Development Expenses

Research and development expenses increased by \$10.5 million to \$103.4 million for the year ended December 31, 2023 from \$92.9 million for the year ended December 31, 2022. Included in research and development expenses for the year ended December 31, 2023, was \$12.6 million of non-cash expense related to stock-based compensation expense, including employee stock options, compared to \$11.5 million for the year ended December 31, 2022. The increase in research and development expense was due to the timing of our clinical development programs along with an increase in non-cash stock-based compensation expense. Research and development expenses may fluctuate from period to period depending upon the stage of certain projects and the level of preclinical and clinical trial-related activities.

Research and development expenses by program are summarized in the table below:

(in thousands)	Year ended December 31,	
	2023	2022
PRT3789.....	\$ 9,738	\$ -
PRT2527.....	7,573	4,030
PRT1419 (Oral and IV).....	8,356	7,709
PRT3645.....	4,809	—
PRMT5 (PRT543 and PRT811).....	(243)	13,275
Discovery programs.....	20,917	25,150
Internal costs, including personnel related.....	52,243	42,725
	<u>\$ 103,393</u>	<u>\$ 92,889</u>

#### General and Administrative Expenses

General and administrative expenses decreased by \$1.8 million to \$28.9 million for the year ended December 31, 2023 from \$30.7 million for the year ended December 31, 2022. Included in the general and administrative expenses for the year ended December 31, 2023, was \$13.0 million of non-cash expense related to stock-based compensation expense, including employee stock options, as compared to \$13.6 million for the same period in 2022. The decrease in general and administrative expense was primarily due to our continued management of general and administrative expenses.

#### Other Income, net

Other income, net increased by \$2.3 million to \$10.4 million for the year ended December 31, 2023 from \$8.1 million for the year ended December 31, 2022, primarily due to interest earned on the investment of our cash proceeds as a result of higher interest rates and higher investment balances as well as the receipt and recognition of research and development tax credits from the State of Delaware during 2023.

## Liquidity and Capital Resources

### Overview

Since our inception, we have not recognized any revenue and have incurred operating losses and negative cash flows from our operations. We have not yet commercialized any product and we do not expect to generate revenue from sales of

any products for several years, if at all. Since our inception, we have funded our operations through the sale of convertible preferred stock and common stock. As of December 31, 2023, we had \$232.9 million in cash, cash equivalents, and marketable securities and had an accumulated deficit of \$456.4 million. We expect our existing cash, cash equivalents, and marketable securities will enable us to fund our operating expense and capital expenditures into 2026. We have based these estimates on assumptions that may prove to be imprecise, and we could utilize our available capital resources sooner than we expect.

During the second quarter of 2023, we sold 6,761,200 shares of common stock which comprised of (i) 5,312,978 shares of voting common stock and (ii) 1,448,222 shares of non-voting common stock at a price of \$5.75 per share and to certain investors in lieu of common stock, we sold pre-funded warrants to purchase 12,895,256 shares of voting common stock at a price of \$5.7499 per pre-funded warrant, resulting in gross proceeds of \$113.0 million. We incurred offering costs of \$2.6 million, of which \$0.3 million were previously paid and deferred, which resulted in net proceeds of \$110.4 million. The purchase price per share of each pre-funded warrant represents the per share offering price for the common stock, minus the \$0.0001 per share exercise price of such pre-funded warrant. Of the voting common stock sold, 2,264,456 were purchased by our underwriters in connection with a 30-day option at a price of \$5.75 per share.

During the fourth quarter of 2023, we sold in a private placement pre-funded warrants to purchase 7,936,759 shares of voting common stock at a price of \$3.1499 per pre-funded warrant, resulting in net proceeds of \$24.8 million after deducting offering costs of \$0.2 million.

### ***Funding Requirements***

Our primary use of cash is to fund operating expenses, primarily research and development expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable, accrued expenses and prepaid expenses.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

- the scope, timing, progress and results of discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs of manufacturing our product candidates for clinical trials and in preparation for marketing approval and commercialization;
- the extent to which we enter into collaborations or other arrangements with additional third parties in order to further develop our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs and fees associated with the discovery, acquisition or in-license of additional product candidates or technologies;
- expenses needed to attract and retain skilled personnel;
- costs associated with being a public company;
- the costs required to scale up our clinical, regulatory and manufacturing capabilities;
- the costs of future commercialization activities, if any, including establishing sales, marketing, manufacturing and distribution capabilities, for any of our product candidates for which we receive marketing approval; and
- revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval.

We will need additional funds to meet operational needs and capital requirements for clinical trials, other research and development expenditures, and business development activities. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies.

In March 2023, we filed a prospectus supplement to our existing shelf registration statement on Form S-3, or the Shelf Registration Statement. The Shelf Registration Statement permits the offering of up to \$400.0 million aggregate dollar amount of shares of our common stock or preferred stock, debt securities, warrants to purchase our common stock, preferred stock or debt securities, subscription rights to purchase our common stock, preferred stock or debt securities and/or units consisting of some or all of these securities, in one or more offerings and in any combination. In March 2023, in connection with filing a prospectus supplement to our Shelf Registration Statement, we entered into an Open Market Sales Agreement<sup>SM</sup>, or the Sales Agreement, with Jefferies LLC, as the sales agent, pursuant to which we may offer and sell shares of our common stock having an aggregate offering amount of up to \$75.0 million. The \$75.0 million of common stock that may be issued and sold pursuant to the Sales Agreement is included in the \$400.0 million of securities that may be issued and sold pursuant to the Shelf Registration Statement. We will pay Jefferies LLC a commission rate of up to 3.0% of the gross proceeds from the sale of any shares of common stock pursuant to the Sales Agreement. We have \$75.0 million remaining under the Sales Agreement.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, reduce or terminate our research, product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

### ***Cash Flows***

The following table shows a summary of our cash flows for the periods indicated:

<b>(in thousands)</b>	<b>Years ended December 31,</b>	
	<b>2023</b>	<b>2022</b>
Net cash used in operating activities.....	\$ (107,063)	\$ (83,729)
Net cash provided by (used in) investing activities .....	(34,646)	81,691
Net cash provided by financing activities.....	136,395	815
Net decrease in cash and cash equivalents.....	\$ (5,314)	\$ (1,223)

### ***Operating Activities***

During the year ended December 31, 2023, we used \$107.1 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$121.8 million along with a \$10.5 million net increase in our operating assets and liabilities offset by noncash charges of \$25.2 million, which consisted of \$25.6 million in stock-based compensation. The primary use of cash was to fund our operations related to the development of our product candidates.

During the year ended December 31, 2022, we used \$83.7 million of cash in operating activities. Cash used in operating activities reflected our net loss of \$115.4 million, offset by a \$0.9 million net decrease in our operating assets and liabilities and noncash charges of \$30.8 million, which consisted of \$25.1 million in stock-based compensation, \$2.6 million in amortization of premiums and discounts on marketable securities, \$1.7 million noncash lease expense, and \$1.3 million in depreciation. The primary use of cash was to fund our operations related to the development of our product candidates.

### ***Investing Activities***

During the year ended December 31, 2023 we used \$34.6 million of cash in investing activities primarily due to net purchases of marketable securities of \$31.1 million. During the year ended December 31, 2022 investing activities provided \$81.7 million of cash primarily due to net maturities of marketable securities of \$84.7 million.

### *Financing Activities*

During the year ended December 31, 2023, financing activities provided \$136.4 million which was primarily the result of \$135.7 million in proceeds received from the sale of common stock and pre-funded warrants, net of issuance costs. During the year ended December 31, 2022, financing activities provided \$0.8 million due to the exercise of stock options and purchases of stock under the Employee Stock Purchase Plan.

### **Contractual obligations and other commitments**

We have one operating lease for office and lab space. Our leased facility includes approximately 81,000 rentable square feet and has an initial term of 162 months with 3 five-year extension options and certain expansion rights. The gross obligation for our operating lease over the next twelve months is \$1.6 million and we expect to make the total lease payments of \$43.2 million through May 2037. See Note 8 to our financial statements included elsewhere in this Annual Report on Form 10-K for additional information.

### **Critical Accounting Estimates**

This management's discussion and analysis of financial condition and results of operations is based on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires management 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 financial statements and the reported amounts of revenues and expenses during the reporting periods. On an ongoing basis, management evaluates its estimates and judgments. Management bases its estimates and judgments on historical experience and on various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

We regard an accounting estimate or assumption underlying our financial statements as a "critical accounting estimate" if:

- the nature of the estimate or assumption is material due to the level of subjectivity and judgment necessary to account for highly uncertain matters or the susceptibility of such matters to change; and
- the impact of the estimates and assumptions on financial condition or operating performance is material.

While our significant accounting policies are described in more detail in Note 3 (Summary of Significant Accounting Policies) to our audited financial statements included elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies are the most critical to the judgments and estimates used in the preparation of our financial statements.

### ***Research and Development Expenses***

Research and development expenses consist primarily of costs incurred in connection with the development of our product candidates. We expense research and development costs as incurred.

We accrue an expense for preclinical studies and clinical trial activities performed by our CROs and vendors based upon estimates of the proportion of work completed. We determine the estimates by reviewing contracts, vendor agreements and purchase orders, and through discussions with our internal clinical personnel and external service providers as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services. However, actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan.

We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known at that time. If the actual timing of the performance of services or the level of effort varies from the estimate, we will adjust the accrual accordingly. Nonrefundable advance payments for goods and services, including fees for clinical trial expenses, process development or manufacturing and distribution of clinical supplies that will be used in future research and development activities, are deferred and recognized as expense in the period that the related goods are consumed or services are performed.

## ***Share-Based Compensation***

We recognize compensation costs related to share-based awards granted to employees and directors, including stock options and vesting restricted stock, based on the estimated fair value of the awards on the date of grant. We estimate the grant date fair value of stock options, and the resulting stock-based compensation, using the Black-Scholes option-pricing model. The grant date fair value of the stock-based awards is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective awards.

We estimate the fair value of stock options using the Black-Scholes option-pricing model, which requires assumptions, including volatility, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options, and our expected dividend yield. Certain assumptions used in our Black-Scholes option-pricing model represent management's best estimates and involve a number of variables, uncertainties and assumptions and the application of management's judgment, as they are inherently subjective. If any assumptions change, our stock-based compensation expense could be materially different in the future.

These subjective assumptions are estimated as follows:

*Expected volatility*—Prior to becoming a public company in 2020, we did not have any trading history for our common stock; accordingly, the expected volatility was estimated based on the average volatility for comparable publicly traded biotechnology companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle or area of specialty. As a public company we have computed the historical volatility of our own stock price and will continue to use the average volatility for comparable publicly traded biotechnology companies until we have ample trading history of our own stock commensurate with the estimated expected term of our options.

*Expected Term*—The expected term represents the period that stock-based awards are expected to be outstanding. The expected term for option grants is determined using the simplified method. The simplified method deems the expected term to be the midpoint between the vesting date and the contractual life of the stock-based awards.

## **JOBS Act Accounting Election**

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies.

We have elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. 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 will remain an emerging growth company until the earliest of (1) the last day of our first fiscal year (a) in which we have total annual gross revenues of at least \$1.235 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30<sup>th</sup>, (2) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period and (3) December 31, 2025.

## **Recent Accounting Pronouncements**

See Note 3 to our financial statements included elsewhere in this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our financial statements.

## **Emerging Growth Company and Smaller Reporting Company Status**

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an “emerging growth company” can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, 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. We have elected to avail ourselves of this exemption from complying with new or revised accounting standards and, therefore, will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. 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.

Subject to certain conditions, as an emerging growth company, we may rely on certain other exemptions and reduced reporting requirements, including without limitation, exemption to the requirements for providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act. We will remain an emerging growth company until the earlier to occur of (a) the last day of the fiscal year (i) following the fifth anniversary of the completion of our IPO, (ii) in which we have total annual gross revenues of at least \$1.235 billion or (iii) in which we are deemed to be a "large accelerated filer" under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30th, or (b) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than \$700.0 million and our annual revenue is less than \$100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company after if either (i) the market value of our stock held by non-affiliates is less than \$250.0 million or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than \$700.0 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. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

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

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

#### **Item 8. Financial Statements and Supplementary Data.**

## INDEX TO FINANCIAL STATEMENTS

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## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and the Board of Directors of Prelude Therapeutics Incorporated

### Opinion on the Financial Statements

We have audited the accompanying balance sheets of Prelude Therapeutics Incorporated (the Company) as of December 31, 2023 and 2022, the related statements of operations and comprehensive loss, changes in stockholders' equity and cash flows for the years then ended, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2023 and 2022, and the results of its operations and its cash flows for 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 2019.

Philadelphia, Pennsylvania

February 15, 2024

**PRELUDE THERAPEUTICS INCORPORATED**

**BALANCE SHEETS**

(in thousands, except share and per share data)	December 31,	
	2023	2022
<b>Assets</b>		
Current assets:		
Cash and cash equivalents .....	\$ 25,291	\$ 30,605
Marketable securities .....	207,644	171,123
Prepaid expenses and other current assets .....	2,654	2,652
Total current assets .....	235,589	204,380
Restricted cash .....	4,044	4,044
Property and equipment, net .....	7,325	4,908
Right-of-use asset .....	30,412	1,792
Prepaid expenses and other non-current assets .....	295	5,376
Total assets .....	\$ 277,665	\$ 220,500
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable .....	\$ 4,580	\$ 6,777
Accrued expenses and other current liabilities .....	15,768	13,093
Operating lease liability .....	1,481	1,832
Total current liabilities .....	21,829	21,702
Other liabilities .....	3,339	3,361
Operating lease liability .....	15,407	—
Total liabilities .....	40,575	25,063
Commitments (note 8)		
Stockholders' equity:		
Voting common stock, \$0.0001 par value: 487,149,741 shares authorized; 42,063,995 and 36,496,994 shares issued and outstanding at December 31, 2023 and 2022, respectively .....	4	4
Non-voting common stock, \$0.0001 par value: 12,850,259 shares authorized; 12,850,259 and 11,402,037 shares issued and outstanding at December 31, 2023 and 2022, respectively .....	1	1
Additional paid-in capital .....	693,252	531,682
Accumulated other comprehensive income (loss) .....	223	(1,692)
Accumulated deficit .....	(456,390)	(334,558)
Total stockholders' equity .....	237,090	195,437
Total liabilities and stockholders' equity .....	\$ 277,665	\$ 220,500

See accompanying notes to financial statements.

**PRELUDE THERAPEUTICS INCORPORATED**

**STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS**

(in thousands, except share and per share data)	Year ended December 31,	
	2023	2022
Operating expenses:		
Research and development.....	\$ 103,393	\$ 92,889
General and administrative.....	28,884	30,651
Total operating expenses.....	132,277	123,540
Loss from operations.....	(132,277)	(123,540)
Other income, net.....	10,445	8,102
Net loss.....	\$ (121,832)	\$ (115,438)
Per share information:		
Net loss per share of common stock, basic and diluted.....	\$ (2.02)	\$ (2.44)
Weighted average common shares outstanding, basic and diluted.....	60,357,052	47,371,589
Comprehensive loss		
Net loss.....	\$ (121,832)	\$ (115,438)
Unrealized gain (loss) on marketable securities, net of tax.....	1,915	(981)
Comprehensive loss.....	\$ (119,917)	\$ (116,419)

See accompanying notes to financial statements.

**PRELUDE THERAPEUTICS INCORPORATED**  
**STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY**

	Voting common stock		Non-voting common stock		Additional paid-in capital	Accumulated Other Comprehensive Income (Loss)	Accumulated deficit	Total
	Shares	Amount	Shares	Amount				
(in thousands, except shares)								
<b>Balance at December 31, 2022</b> .....	36,496,994	\$ 4	11,402,037	\$ 1	\$ 531,682	\$ (1,692)	\$ (334,558)	\$ 195,437
Issuance of common stock and prefunded warrants, net of issuance costs of \$2.8 million.....	5,312,978	—	1,448,222	—	135,290	—	—	135,290
Issuance of common stock upon exercise of stock options & vesting of RSUs, net of 3,983 shares withheld for employee taxes.....	84,166	—	—	—	30	—	—	30
Issuance of common stock under ESPP ...	169,857	—	—	—	634	—	—	634
Unrealized gain on marketable securities, net of tax.....	—	—	—	—	—	1,915	—	1,915
Stock-based compensation expense, net of forfeitures of restricted stock.....	—	—	—	—	25,616	—	—	25,616
Net loss.....	—	—	—	—	—	—	(121,832)	(121,832)
<b>Balance at December 31, 2023</b> .....	42,063,995	\$ 4	12,850,259	\$ 1	\$ 693,252	\$ 223	\$ (456,390)	\$ 237,090

	Voting common stock		Non-voting common stock		Additional paid-in capital	Accumulated Other Comprehensive Income (Loss)	Accumulated deficit	Total
	Shares	Amount	Shares	Amount				
(in thousands, except shares)								
<b>Balance at January 1, 2022</b> .....	36,200,299	\$ 4	11,402,037	\$ 1	\$ 505,723	\$ (711)	\$ (219,120)	\$ 285,897
Issuance of common stock upon exercise of stock options & vesting of RSUs.....	222,905	—	—	—	389	—	—	389
Issuance of common stock under ESPP ...	97,206	—	—	—	426	—	—	426
Unrealized loss on marketable securities, net of tax.....	—	—	—	—	—	(981)	—	(981)
Stock-based compensation expense, net of forfeitures of restricted stock.....	(23,416)	—	—	—	25,144	—	—	25,144
Net loss.....	—	—	—	—	—	—	(115,438)	(115,438)
<b>Balance at December 31, 2022</b> .....	36,496,994	\$ 4	11,402,037	\$ 1	\$ 531,682	\$ (1,692)	\$ (334,558)	\$ 195,437

See accompanying notes to financial statements.

**PRELUDE THERAPEUTICS INCORPORATED**

**STATEMENTS OF CASH FLOWS**

(in thousands)	Year ended December 31,	
	2023	2022
Cash flows used in operating activities:		
Net loss .....	\$ (121,832)	\$ (115,438)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization .....	1,169	1,324
Noncash lease expense .....	1,936	1,718
Stock-based compensation .....	25,616	25,144
Amortization of premium and discount on marketable securities, net.....	(3,473)	2,591
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets.....	(297)	(3,843)
Accounts payable .....	(2,270)	(347)
Accrued expenses and other liabilities .....	2,522	6,833
Long-term prepaid expenses and other long-term assets .....	(8,810)	—
Operating lease liabilities .....	(1,624)	(1,711)
Net cash used in operating activities .....	(107,063)	(83,729)
Cash flows (used in) provided by investing activities:		
Purchases of marketable securities .....	(221,633)	(119,223)
Proceeds from maturities of marketable securities.....	190,500	203,933
Purchases of property and equipment .....	(3,513)	(3,019)
Net cash (used in) provided by investing activities.....	(34,646)	81,691
Cash flows provided by financing activities:		
Proceeds from issuance of common stock and pre-funded warrants, net of offering costs .....	135,731	—
Proceeds from issuance of common stock in connection with the exercise of stock options .....	47	389
Proceeds from the issuance of common stock under ESPP .....	634	426
Payment of withholding taxes related to stock-based compensation to employees..	(17)	—
Net cash provided by financing activities .....	136,395	815
Net decrease in cash and cash equivalents .....	(5,314)	(1,223)
Cash, cash equivalents and restricted cash at beginning of year .....	34,649	35,872
Cash, cash equivalents and restricted cash at end of year .....	\$ 29,335	\$ 34,649
Supplemental disclosures:		
Operating lease right-of-use assets obtained in exchange for operating lease liabilities .....	\$ 16,680	\$ 1,803
Property and equipment in accounts payable .....	\$ 163	\$ 90
Unrealized gain (loss) on marketable securities.....	\$ 1,915	\$ (981)
Offering costs in accrued expenses and other current liabilities.....	\$ 131	\$ —

See accompanying notes to financial statements.

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS

#### 1. Nature of Operations

Prelude Therapeutics Incorporated (the “Company”) is a clinical-stage fully integrated oncology company built on a foundation of drug discovery excellence to deliver novel precision cancer medicines to underserved patients. Since beginning operations in 2016, the Company has devoted substantially all its efforts to research and development, conducting preclinical and clinical studies, recruiting management and technical staff, administration, and raising capital.

#### 2. Risks and Liquidity

The Company is subject to a number of risks common to early-stage companies in the biotechnology industry. Principal among these risks are the uncertainties in the development process, development of the same or similar technological innovations by competitors, protection of proprietary technology, dependence on key personnel, compliance with government regulations and approval requirements, and the need to obtain additional financing to fund operations. Product candidates currently under development will require significant additional research and development efforts, including extensive pre-clinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure, and extensive compliance-reporting capabilities. There can be no assurance that the Company’s research and development will be successfully completed, that adequate protection for the Company’s technology will be obtained, that any products developed will obtain necessary government regulatory approval, or that any approved products will be commercially viable. The Company operates in an environment of rapid change in technology and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees, consultants and contractors.

Since its inception, the Company has incurred operating losses and had an accumulated deficit of \$456.4 million at December 31, 2023. The Company has no revenue to date and devotes its efforts to research and development. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates currently in development.

The Company believes that its cash, cash equivalents and marketable securities as of December 31, 2023 will be sufficient to fund its operating expenses and capital expenditure requirements into 2026.

To fund its operating expenses and capital expenditure requirements after that date, the Company plans to seek additional funding through public or private equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into strategic alliances or other arrangements on favorable terms, or at all. The terms of any financing may adversely affect the holdings or the rights of the Company’s stockholders. If the Company is unable to obtain funding, the Company could be required to delay, reduce or eliminate research and development programs, product portfolio expansion or future commercialization efforts, which could adversely affect its business prospects.



# PRELUDE THERAPEUTICS INCORPORATED

## NOTES TO FINANCIAL STATEMENTS — Continued

### 3. Summary of Significant Accounting Policies

#### *Basis of Presentation*

The accompanying financial statements have been prepared in accordance with generally accepted accounting principles (“GAAP”). Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification (“ASC”) and Accounting Standards Updates (“ASU”) promulgated by the Financial Accounting Standards Board (“FASB”).

#### *Use of Estimates*

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and contingent liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

Estimates and assumptions are periodically reviewed, and the effects of the revisions are reflected in the accompanying financial statements in the period they are determined to be necessary. The most significant estimate relates to accrued clinical trial expenses.

#### *Concentration of Credit Risk*

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist of cash, cash equivalents, and marketable securities. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and believes it is not exposed to significant credit risk beyond the normal credit risk associated with commercial banking relationships.

#### *Segment Information*

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views and manages its operations as a single operating segment.

#### *Fair Value of Financial Instruments*

Management believes that the carrying amounts of the Company’s financial instruments, including cash, restricted cash, accounts payable, and accrued expenses, approximate fair value due to the short-term nature of these instruments.

#### *Cash, Cash Equivalents and Restricted cash*

The Company’s cash equivalents include short-term highly liquid investments with an original maturity of 90 days or less when purchased and are carried at fair value in the accompanying balance sheets.

Restricted cash comprises a letter of credit with Silicon Valley Bank for the benefit of the landlord in connection with the Company’s new lease facility. See Note 8 (Commitments) for further details.

The following table provides a reconciliation of cash and cash equivalents and restricted cash reported within the balance sheet that total to the amounts shown in the statement of cash flows:

(in thousands)	December 31,	
	2023	2022
Cash and cash equivalents .....	\$ 25,291	\$ 30,605
Restricted cash .....	4,044	4,044
Total cash, cash equivalents, and restricted cash shown in statement of cash flows.....	\$ 29,335	\$ 34,649

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

#### *Marketable Securities*

The Company's marketable securities consist of investments in corporate debt securities, United States, or U.S., government debt securities, and agency securities that are classified as available-for-sale. The securities are carried at fair value with the unrealized gains and losses, net of tax, included in accumulated other comprehensive income (loss), a component of stockholders' equity. Realized gains and losses as well as credit losses, if any, on marketable securities are included in the Company's statements of operations. The Company classifies marketable securities that are available for use in current operations as current assets on the balance sheets.

#### *Property and Equipment*

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation expense is recognized using the straight-line method over the estimated useful life of the asset, ranging from 5-7 years as follows:

Fixed Asset Type	Estimated useful life
Lab equipment	5 years
IT equipment	5 years
Furniture and fixtures	7 years

Leasehold improvements are amortized over the shorter of the estimated useful life of the assets or the remaining lease term.

Expenditures for repairs and maintenance of assets are charged to expense as incurred, while major betterments are capitalized. Upon retirement or sale, the cost and related accumulated depreciation of assets disposed of are removed from the accounts and any resulting gain or loss is included in the statements of operations.

The Company reviews long-lived assets, such as property and equipment, for impairment when events or changes in circumstances indicate the carrying amount of the assets may not be recoverable. If indicators of impairment are present, the assets are tested for recoverability by comparing the carrying amount of the assets to the related estimated future undiscounted cash flows that the assets are expected to generate. If the expected cash flows are less than the carrying value of the asset, then the asset is considered to be impaired and its carrying value is written down to fair value, based on the related estimated discounted future cash flows.

#### *Leases*

The Company accounts for leases in accordance with ASC Topic 842, *Leases*. The Company's lease for office and laboratory space located in Wilmington, DE is classified as an operating lease. The lease results in an operating right-of-use (ROU) asset, a current operating lease liability, and a non-current operating lease liability in the balance sheet and has a remaining lease term of 162 months. The Company does not have any financing leases. Leases with a term of 12 months or less are considered short-term and a ROU asset and lease obligation are not recognized.

ROU assets represent the right to use an underlying asset for the lease term and the lease liabilities represent an obligation to make lease payments arising from the lease, measured at the present value of the lease payments not yet paid discounted using the discount rate for the lease established at the lease commencement date. The operating lease ROU asset also includes any prepaid lease payments made. Lease expense is recognized over the expected lease term on a straight-line basis.

#### *Comprehensive loss*

Comprehensive loss includes net loss and certain changes in stockholders' equity that are excluded from net loss. The Company's comprehensive loss for the years ended December 31, 2023 and 2022 comprised net loss and unrealized gain or loss on marketable securities.

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

#### *Stock-Based Compensation*

The Company measures share-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards.

Estimating the fair value of share-based awards requires the input of subjective assumptions, including, for stock options, the expected life of the options and stock price volatility. The Company accounts for forfeitures for stock option awards as they occur. The Company uses the Black-Scholes option pricing model to value its stock option awards. The assumptions used in estimating the fair value of share-based awards represent management's estimate and involve inherent uncertainties and the application of management's judgment. As a result, if factors change and management uses different assumptions, share-based compensation expense could be materially different for future awards.

The expected life of the stock options is estimated using the "simplified method", as the Company has limited historical information from which to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock option grants. The simplified method is the midpoint between the vesting period and the contractual term of the option. For stock price volatility, the Company uses its own historical volatility along with comparable public companies as a basis for its expected volatility to calculate the fair value of option grants. The risk-free rate is based on the U.S. Treasury yield curve commensurate with the expected life of the option.

#### *Grant Income and Research and Development Tax Credits*

The Company recognizes grants related to income and Delaware research and development tax credits in other income, net in the statements of operations when the necessary qualifying conditions, as stated in the agreements, are met and all contingencies have been resolved. For the years ended December 31, 2023 and 2022, the Company recorded other income of \$1.5 million and \$6.1 million, respectively. The Company recognizes grants related to assets as deferred income on the balance sheet. The deferred income is then recognized as grant income over the useful life of the related assets.

#### *Research and Development*

Research and development costs are expensed as incurred. Research and development expenses consist principally of personnel costs, including salaries, stock-based compensation, and benefits of employees, and other operational costs related to the Company's research and development activities, including allocated facility-related expenses and external costs of outside vendors, such as clinical research organizations and clinical manufacturing organizations, and other direct and indirect costs.

Management makes estimates of the Company's accrued research and development expenses as of each balance sheet date in the Company's financial statements based on facts and circumstances known to the Company at that time. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual accordingly. Nonrefundable advance payments for goods and services, including fees for process development or manufacturing and distribution of clinical supplies that will be used in future research and development activities, are deferred and recognized as expense in the period that the related goods are consumed or services are performed.

#### *Income Taxes*

Income taxes are accounted for under the asset-and-liability method as required by FASB ASC Topic 740, *Income Taxes* ("ASC 740"). Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted 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 on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period corresponding to the enactment date. Under ASC 740, a valuation allowance is required when it is more likely than not all or some portion of the deferred tax assets will not be realized through generating sufficient future taxable income.

FASB ASC Subtopic 740-10, *Accounting for Uncertainty of Income Taxes*, ("ASC 740-10") defines the criterion an individual tax position must meet for any part of the benefit of the tax position to be recognized in financial statements prepared in conformity with GAAP. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not such tax position will be sustained on examination by the taxing authorities, based solely on the

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

technical merits of the respective tax position. The tax benefits recognized in the financial statements from such a tax position should be measured based on the largest benefit having a greater than 50% likelihood of being realized upon ultimate settlement with the tax authority. In accordance with the disclosure requirements of ASC 740-10, the Company's policy on income statement classification of interest and penalties related to income tax obligations is to include such items as a component of income tax expense.

#### *Net Loss Per Share*

Basic net loss per share of common stock is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during each period, including pre-funded warrants to purchase shares of common stock that were issued in a financing transaction in 2023 (Note 9). The weighted-average number of shares of common stock outstanding used in the basic net loss per share calculation does not include unvested restricted stock awards as these instruments are considered contingently issuable shares until they vest. Diluted net loss per share of common stock includes the effect, if any, from the potential exercise of securities, such as stock options, and the effect from unvested restricted stock awards and restricted stock units which would result in the issuance of incremental shares of common stock. For diluted net loss per share, the weighted-average number of shares of common stock is the same for basic net loss per share due to the fact that when a net loss exists, dilutive securities are not included in the calculation as the impact is anti-dilutive. The Company's unvested restricted stock awards entitle the holder to participate in dividends and earnings of the Company, and, if the Company were to recognize net income, it would have to use the two-class method to calculate earnings per share. The two-class method is not applicable during periods with a net loss, as the holders of the unvested restricted stock awards have no obligation to fund losses.

The following potentially dilutive securities have been excluded from the computation of diluted weighted-average shares of common stock outstanding, as they would be anti-dilutive:

	December 31,	
	2023	2022
Unvested restricted stock awards.....	27,008	201,716
Unvested restricted stock units .....	103,750	165,000
Stock options.....	11,898,446	9,390,930
	<u>12,029,204</u>	<u>9,757,646</u>

Amounts in the above table reflect the common stock equivalents.

#### *Recently Issued Accounting Pronouncements*

##### *Emerging Growth Company Status*

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act, until such time as those standards apply to private companies. The Company has elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. The Company will remain an emerging growth company until the earliest of (i) the last day of the Company's first fiscal year (a) in which the Company has total annual gross revenues of at least \$1.235 billion, or (b) in which the Company is deemed to be a large accelerated filer, which means the market value of the Company's common stock that is held by non-affiliates exceeds \$700.0 million as of the prior June 30, (ii) the date on which the Company has issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period and (iii) December 31, 2025. As a result, these financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

##### *Recently Adopted Accounting Pronouncements*

In August 2020, the FASB issued ASU Update 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): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity (ASU 2020-06)* ("ASU 2020-06"). ASU 2020-06 eliminated the beneficial conversion and cash conversion accounting models in ASC 470-20 which required separate

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

accounting for embedded conversion features and simplified the settlement assessment to determine whether an instrument qualifies for equity classification. The Company early adopted the new standard on January 1, 2023. The adoption did not have a material impact on the financial statements.

#### *Accounting guidance not yet adopted*

In December 2023, the FASB issued ASU Updated No. 2023-09, *Income Taxes - Improvements to Income Tax Disclosures*. ASU 2023-09 requires enhanced income tax disclosures related to the rate reconciliation and income taxes paid information. For public business entities, the amendments in this Update are effective for annual periods beginning after December 15, 2024 with early adoption permitted. The Company is currently evaluating the impact of this standard but does not expect that it will have a material impact on the financial statements and related disclosures.

#### 4. Marketable Securities

The following is a summary of the Company's marketable securities as of December 31, 2023 and 2022.

(in thousands)	Amortized Cost	Gross unrealized gain	Gross unrealized loss	Fair Value
<b>December 31, 2023:</b>				
Marketable securities				
Agency securities.....	\$ 10,431	\$ 19	\$ —	\$ 10,450
Corporate debt securities .....	67,806	193	(20)	67,979
U.S. government securities.....	129,184	72	(41)	129,215
Total.....	<u>\$ 207,421</u>	<u>\$ 284</u>	<u>\$ (61)</u>	<u>\$ 207,644</u>
<b>December 31, 2022:</b>				
Marketable securities				
Corporate debt securities .....	\$ 163,208	\$ 7	\$ (1,672)	\$ 161,543
U.S. government securities.....	9,607	—	(27)	9,580
Total.....	<u>\$ 172,815</u>	<u>\$ 7</u>	<u>\$ (1,699)</u>	<u>\$ 171,123</u>

The Company's marketable securities generally have contractual maturity dates of 21 months or less. As of December 31, 2023, the Company had 19 securities with a total fair market value of \$75.6 million in an unrealized loss position. The Company believes that any unrealized losses associated with the decline in value of its securities is temporary and is primarily related to the change in market interest rates since purchase and believes that it is more likely than not that it will be able to hold its debt securities to maturity.

#### 5. Fair Value of Financial Instruments

Fair value is the price that could be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Fair value determination in accordance with applicable accounting guidance requires that a number of significant judgments be made. Additionally, fair value is used on a nonrecurring basis to evaluate assets for impairment or as required for disclosure purposes by applicable accounting guidance on disclosures about fair value of financial instruments. Depending on the nature of the assets and liabilities, various valuation techniques and assumptions are used when estimating fair value. The Company follows the provisions of ASC 820, Fair Value Measurement, for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements be classified and disclosed in one of the following three categories:

- *Level 1:* Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities.
- *Level 2:* Quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liabilities.
- *Level 3:* Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

The following fair value hierarchy table presents information about the Company's assets and liabilities measured at fair value on a recurring basis:

(in thousands)	Fair value measurement at reporting date using		
	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
<b>December 31, 2023:</b>			
Assets:			
Cash equivalents (Money Market Funds).....	\$ 24,369	\$ —	\$ —
Marketable securities			
Agency securities.....		10,450	
Corporate debt securities .....	—	67,979	—
U.S. government securities.....	—	129,215	—
Total.....	\$ 24,369	\$ 207,644	\$ —
<b>December 31, 2022:</b>			
Assets:			
Cash equivalents (Money Market Funds).....	\$ 25,996	\$ —	\$ —
Marketable securities			
Corporate debt securities .....	—	161,543	—
U.S. government securities.....	—	9,580	—
Total.....	\$ 25,996	\$ 171,123	\$ —

**6. Property and Equipment**

Property and equipment consisted of the following:

(in thousands)	December 31,	
	2023	2022
Lab equipment.....	\$ 6,643	\$ 5,588
Leasehold improvements.....	1,582	875
IT equipment .....	470	40
Furniture and fixtures .....	1,858	87
Construction in progress.....	338	1,637
	10,891	8,227
Less accumulated depreciation.....	(3,566)	(3,319)
Property and equipment, net.....	\$ 7,325	\$ 4,908

**7. Accrued Expenses and Other Current Liabilities**

Accrued expenses and other current liabilities consisted of the following:

(in thousands)	December 31,	
	2023	2022
Compensation and related benefits .....	\$ 9,157	\$ 5,682
Research and development .....	5,666	6,887
Other .....	945	524
	\$ 15,768	\$ 13,093

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

**8. Commitments**

*Leases*

The Company leased office and laboratory space in Wilmington, Delaware under a noncancelable lease (the “Lease”) for which the lease term ended on December 31, 2023. The discount rate used to account for the Company’s operating lease under ASC 842, Leases, was the Company’s estimated incremental borrowing rate of 9.5%.

In 2021, the Company entered into a lease agreement for office and lab space at Chestnut Run Plaza in Wilmington, Delaware (the “Chestnut Run Lease”). The premises includes approximately 81,000 rentable square feet and has an initial term of 162 months with 3 five-year extension options and certain expansion rights. Neither the option to extend nor the expansion rights were recognized as part of the Company’s measurement of the ROU asset and operating lease liability as of December 31, 2023. Under the terms of the Chestnut Run Lease, the landlord provided an allowance towards the cost of completing tenant improvements for the premises. The Company concluded that the improvements resulting from both the landlord’s build-out and the tenant improvements are the landlord’s assets for accounting purposes. Costs incurred by the Company related to tenant improvements in excess of the landlord’s allowance have been treated as prepaid rent and increased the right-of-use asset on the commencement date. The Chestnut Run Lease commenced for accounting purposes in December 2023 when the Company took control of the leased space. On the commencement date, the Company recorded approximately \$30.6 million and \$16.7 million of right-of-use asset and lease liability, respectively. The right-of-use asset includes approximately \$13.9 million related to prepaid rent which was reclassified from long-term prepaid assets. The discount rate used to account for the Company’s operating lease under ASC 842, Leases, is the Company’s estimated incremental borrowing rate of 15.0%. The Company’s incremental borrowing rate reflects a collateralized borrowing with a similar term and amount as the Chestnut Run Lease.

Lease cost for the year ended December 31, 2023 was \$2.5 million, including \$0.2 million of short-term lease cost. Lease cost for the year ended December 31, 2022 was \$2.1 million, including \$0.3 million of short-term lease cost. Cash paid for amounts included in the measurement of operating lease liabilities for the years ended December 31, 2023 and 2022 was \$1.9 million and \$1.8 million, respectively.

As of December 31, 2023 the estimated rent payments related to the Chestnut Run Lease are as follows:

<u>(in thousands)</u>		
2024 .....	\$	1,615
2025 .....		2,746
2026 .....		2,979
2027 .....		3,054
2028 .....		3,130
Thereafter .....		29,635

The Company paid a security deposit in the form of a letter of credit with Silicon Valley Bank of \$4.0 million which is included in the balance sheet as restricted cash as of December 31, 2023 and 2022. The security deposit may be reduced to \$0.5 million over time in accordance with the terms of the Chestnut Run Lease.

In connection with the Company’s expansion of operations in the State of Delaware, the Company was approved for a grant from the State of Delaware in 2021 that will provide up to \$5.5 million in reimbursements over three years for the development of lab space in addition to increasing jobs in Delaware to meet specific targeted levels through 2023. During the third quarter of 2022, the Company was approved for an additional grant from the State of Delaware for the development of lab space in the amount of \$1.0 million. In 2022, the Company received cash of \$3.4 million from the grants for the development of lab space. The Company has met the minimum requirements stated in the grant agreement in order to not be required to pay back any portion of the \$3.4 million disbursed. The Company has deferred the recognition of these grant funds as they relate to capitalized costs and has classified them as long-term liabilities on the balance sheet. In December 2023, the Company began to recognize the grant funds in other income and will continue to do so over the useful life of the related assets. If the Company leaves the State of Delaware within five years of the disbursement, the Company is required to return an amount equal to the amount of grant funds disbursed on a pro-rated basis.

## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

#### *Employment Agreements*

The Company entered into employment agreements with key personnel providing for compensation and severance in certain circumstances, as defined in the respective employment agreements.

#### *401(k) Defined Contribution Plan*

The Company sponsors a 401(k) defined-contribution plan covering all employees. Participants are permitted to contribute up to 100% of their eligible annual pretax compensation up to an established federal limit on aggregate participant contributions. The Company provides a match with a maximum amount of 3% of the participant's compensation. During the years ended December 31, 2023 and 2022 the Company made matching contributions of \$0.7 million and \$0.6 million, respectively.

#### *Research Collaboration Agreement*

In November 2023, the Company entered into a multi-year, multi-program agreement with AbCellera to jointly discover, develop, and commercialize novel oncology medicines for up to five programs. Under the terms of the agreement, AbCellera will lead manufacturing activities and the Company will lead clinical development and global commercialization, subject to AbCellera's option to co-promote any resulting commercial products in the United States. If, at any point one party in the collaboration opts-out of future co-development cost sharing, that party will be entitled to a royalty from commercialization of the collaboration target, dependent on the proportion of their co-development contributions compared to the total development costs of a target as defined within the agreement. The Company concluded that the agreement with AbCellera will be accounted for under the scope of ASC 808 as both parties will actively participate in joint operating activities and are exposed to significant risks and rewards. Under ASC 808, certain transactions between collaborative arrangement participants should follow the accounting for revenue under ASC 606 when the collaborative arrangement participant is a customer for a distinct good or service. The Company determined that co-development arrangement as defined in our agreement with AbCellera does not meet the definition of a customer as defined by ASC 606. As a result, these activities will be accounted for as research and development costs. Costs related to the AbCellera collaboration were not material for the year ended December 31, 2023.

#### *Other Research and Development Arrangements*

The Company enters into agreements with CROs to assist in the performance of research and development activities. Expenditures to CROs will represent a significant cost in clinical development for the Company.

### **9. Common Stock**

The Company has two classes of common stock; "voting common stock" and "non-voting common stock." The holders of the voting common stock are entitled to one vote for each share of voting common stock held at all meetings of stockholders. Except as otherwise required by law, the holders of non-voting common stock shall not be entitled to vote at any meetings of stockholders (or written actions in lieu of meetings) and the shares of non-voting common stock shall not be included in determining the number of shares voting or entitled to vote on any matter. Unless required by law, there shall be no cumulative voting. Any holder of non-voting common stock may elect to convert each share of non-voting common stock into one fully paid and non-assessable share of voting common stock at any time by providing written notice to the Company; provided that as a result of such conversion, such holder, together with its affiliates and any members of a Schedule 13(d) group with such holder, would not beneficially own in excess of 9.99% of the Company's common stock immediately prior to and following such conversion, unless otherwise as expressly provided for in the Company's restated certificate of incorporation. However, this ownership limitation may be increased (not to exceed 19.99%) or decreased to any other percentage designated by such holder of non-voting common stock upon 61 days' notice to the Company.

#### *2023 financings*

During the second quarter of 2023, the Company sold 6,761,200 shares of its common stock which comprised of (i) 5,312,978 shares of its voting common stock and (ii) 1,448,222 shares of its non-voting common stock at a price of \$5.75 per share and to certain investors in lieu of common stock, the Company sold pre-funded warrants to purchase 12,895,256 shares of voting common stock at a price of \$5.7499 per pre-funded warrant, resulting in gross proceeds to the Company of \$113.0



## PRELUDE THERAPEUTICS INCORPORATED

### NOTES TO FINANCIAL STATEMENTS — Continued

million. Of the voting common stock issued, 2,264,456 shares were purchased by the Company's underwriters in connection with a 30-day option at a price of \$5.75 per share. Offering costs of \$2.6 million, of which \$0.3 million were previously paid and deferred, were recorded to additional paid-in capital in the accompanying balance sheets, resulting in net proceeds of \$110.4 million.

During the fourth quarter of 2023, the Company sold in a private placement pre-funded warrants to purchase 7,936,759 shares of voting common stock at a price of \$3.1499 per pre-funded warrant, resulting in net proceeds of \$24.8 million after deducting offering costs of \$0.2 million.

The purchase price per share of each pre-funded warrant represents the per share offering price for the common stock, minus the \$0.0001 per share exercise price of such pre-funded warrant. As of December 31, 2023, no pre-funded warrants had been exercised.

The pre-funded warrants were classified as a component of permanent stockholders' equity within additional paid-in capital and were recorded at the issuance date using a relative fair value allocation method. The pre-funded warrants are equity classified because they (i) are freestanding financial instruments that are legally detachable and separately exercisable from the equity instruments, (ii) are immediately exercisable, (iii) do not embody an obligation for the Company to repurchase its shares, (iv) permit the holders to receive a fixed number of shares of common stock upon exercise, (v) are indexed to the Company's common stock and (vi) meet the equity classification criteria. In addition, such pre-funded warrants do not provide any guarantee of value or return.

#### 10. Stock-Based Compensation

The Company has two equity incentive plans: the 2016 Equity Incentive Plan, as amended, and the 2020 Equity Incentive Plan. New awards can only be granted under the 2020 Equity Incentive Plan (the "Plan"). The total number of shares initially authorized under the Plan was 4,680,000, which was increased on January 1, 2021 and will automatically increase on January 1st of each year, continuing for ten years, in an amount equal to five percent of the total number of shares of the Company's common stock outstanding on December 31st of the preceding calendar year, subject to the discretion of the board of directors or compensation committee to determine a lesser number of shares shall be added for such year. At December 31, 2023, 4,999,564 shares were available for future grants and on January 1, 2024, 2,745,712 shares were added to the Plan. The Plan provides for the granting of common stock, incentive stock options, nonqualified stock options, restricted stock awards, restricted stock units and/or stock appreciation rights to employees, directors, and other persons, as determined by the Company's board of directors. The Company's stock options vest based on the terms in each award agreement, generally over four-year periods with 25% of options vesting after 1 year and then monthly thereafter, and have a term of ten years.

The Company measures stock-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards. The Company recorded stock-based compensation expense in the following expense categories in its accompanying statements of operations:

(in thousands)	Year Ended December 31,	
	2023	2022
Research and development .....	\$ 12,626	\$ 11,549
General and administrative .....	12,990	13,595
	<u>\$ 25,616</u>	<u>\$ 25,144</u>

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

**Stock Options**

The following table summarizes stock option activity for the Plan in the years indicated:

	Number of shares	Weighted average exercise price per share	Weighted average remaining contractual term (years)
Outstanding at January 1, 2022 .....	7,179,482	\$ 15.36	8.66
Granted .....	3,884,429	\$ 7.58	
Exercised .....	(217,905)	\$ 1.78	
Forfeited .....	(1,455,076)	\$ 17.84	
Outstanding at December 31, 2022 .....	<u>9,390,930</u>	\$ 12.08	8.31
Granted .....	3,238,898	\$ 6.68	
Exercised .....	(26,899)	\$ 1.78	
Forfeited .....	(704,483)	\$ 12.58	
Outstanding at December 31, 2023 .....	<u>11,898,446</u>	\$ 10.60	7.77
Exercisable at December 31, 2023 .....	<u>6,084,483</u>	\$ 11.62	6.96

The aggregate intrinsic value of options exercised was \$0.1 million and \$1.1 million during the year ended December 31, 2023 and 2022, respectively. At December 31, 2023, the aggregate intrinsic value of outstanding options and exercisable options was \$4.9 million and \$4.7 million, respectively.

The following table summarizes information about stock options outstanding and exercisable at December 31, 2023 under the Plan:

Range of Exercise Prices	Options Outstanding			Options Exercisable	
	Number Outstanding	Weighted Average Remaining Contractual Life (in years)	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
\$0.31 - \$4.88 .....	3,061,004	6.82	\$ 2.80	2,400,106	\$ 2.40
\$4.89 - \$7.50 .....	3,905,574	8.99	6.57	366,158	5.83
\$7.51 - \$13.04 .....	3,141,601	7.28	11.87	2,149,353	12.19
\$13.05 - \$88.98 .....	1,790,267	7.56	30.51	1,168,866	31.32
	<u>11,898,446</u>			<u>6,084,483</u>	

The weighted-average grant date fair value of options granted was \$4.87 and \$5.49 per share for the years ended December 31, 2023 and 2022, respectively. The Company recorded stock-based compensation expense of \$24.6 million and \$23.9 million for the years ended December 31, 2023 and 2022, respectively, related to stock options. As of December 31, 2023, the total unrecognized compensation expense related to unvested stock option awards was \$36.4 million, which the Company expects to recognize over a weighted-average period of 2.03 years.

The fair value of each option was estimated on the date of grant using the weighted average assumptions in the table below:

	Year Ended December 31,	
	2023	2022
Expected volatility .....	83.57%	84.67%
Risk-free interest rate .....	3.82%	2.73%
Expected life (in years) .....	6.02	6.03
Expected dividend yield .....	—	—

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

***Restricted Stock Awards and Units***

The Company issues restricted stock awards (“RSA”) to employees that generally vest over a four-year period with 25% of awards vesting after 1 year and then monthly thereafter. Any unvested shares will be forfeited upon termination of services. The fair value of an RSA is equal to the fair market value price of the Company’s common stock on the date of grant. RSA expense is recorded on a straight-line basis over the vesting period.

The following table summarizes activity related to RSA stock-based payment awards:

	Number of shares	Weighted- average grant date fair value
Unvested balance at January 1, 2022.....	611,608	\$ 2.29
Vested .....	(386,476)	\$ 2.05
Forfeited.....	(23,416)	\$ 1.89
Unvested balance at December 31, 2022.....	<u>201,716</u>	\$ 2.81
Vested .....	(174,708)	\$ 2.74
Unvested balance at December 31, 2023.....	<u><u>27,008</u></u>	\$ 3.26

The Company recorded stock-based compensation expense of \$0.5 million and \$0.8 million for the years ended December 31, 2023 and 2022, respectively, related to RSAs. As of December 31, 2023, the total unrecognized expense related to all RSAs was \$0.1 million, which the Company expects to recognize over a weighted-average period of 0.24 years.

The Company issues restricted stock units (“RSU”) to employees that generally vest over a four-year period with 25% of awards vesting after 1 year and then quarterly thereafter. Any unvested shares will be forfeited upon termination of services.

The following table summarizes activity related to RSU stock-based payment awards:

	Number of shares	Weighted- average grant date fair value
Outstanding at January 1, 2022.....	20,000	\$ 18.32
Granted.....	150,000	\$ 4.86
Forfeited.....	(5,000)	\$ 18.32
Outstanding at December 31, 2022.....	<u>165,000</u>	\$ 6.08
Vested.....	(61,250)	\$ 5.96
Outstanding at December 31, 2023.....	<u><u>103,750</u></u>	\$ 6.16

The Company recorded stock-based compensation expense of \$0.3 million and \$0.2 million for the years ended December 31, 2023 and 2022, respectively, related to RSUs. At December 31, 2023 the total unrecognized expense related to the RSUs was \$0.6 million, which the Company expects to recognize over 2.12 years.

***Employee Stock Purchase Plan***

The Company has an Employee Stock Purchase Plan (the “ESPP”), which as of December 31, 2023 had 1,619,292 shares of common stock reserved for future issuance. The Company issued 169,857 shares under the ESPP in 2023. The number of shares of the Company’s common stock that may be issued pursuant to rights granted under the ESPP shall automatically increase on January 1st of each year and continuing for ten years beginning in 2021, in an amount equal to one percent of the total number of shares of all classes of the Company’s common stock outstanding on December 31st of the preceding calendar year, subject to the discretion of the board of directors or compensation committee to determine a lesser number of shares shall be added for such year. As such, on January 1, 2024, 549,142 shares were added to the ESPP.

Under the ESPP, eligible employees can purchase the Company’s common stock through accumulated payroll deductions at such times as are established by the compensation committee. Eligible employees may purchase the Company’s common stock at 85% of the lower of the fair market value of the Company’s common stock on the first day of the offering

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

period or on the last day of the offering period. Eligible employees may contribute up to 15% of their eligible compensation. Under the ESPP, a participant may not accrue rights to purchase more than \$25,000 worth of the Company’s common stock for each calendar year in which such right is outstanding.

The ESPP is considered compensatory under the FASB stock compensation rules. Accordingly, share-based compensation expense is determined based on the option’s grant-date fair value as estimated by applying the Black Scholes option-pricing model and is recognized over the withholding period. The Company recognized share-based compensation expense of \$0.3 million for both years ended December 31, 2023 and 2022 related to the ESPP.

**11. Income Taxes**

The tax effects of temporary differences that gave rise to significant portions of the deferred tax assets and liabilities were as follows:

(in thousands)	December 31,	
	2023	2022
Deferred tax assets:		
Net operating loss carryforwards .....	\$ 71,963	\$ 66,067
Research and development credits .....	20,555	15,234
Research and development capitalization .....	39,867	19,900
Stock-based compensation .....	12,990	8,725
Accrued expense .....	2,539	1,190
Lease liabilities .....	4,715	511
Gross deferred tax assets .....	152,629	111,627
Less: valuation allowance .....	(147,616)	(111,053)
Total deferred tax asset .....	5,013	574
Deferred tax liability		
Right-of-use assets .....	(4,641)	(500)
Depreciation .....	(372)	(74)
Total deferred tax liabilities .....	(5,013)	(574)
Net deferred tax assets .....	\$ —	\$ —

The deferred tax assets as of December 31, 2023 and 2022, includes capitalized research and development expenses of \$39.9 million and \$19.9 million, respectively. The Tax Cuts and Jobs Act passed in 2017 included a provision which requires taxpayers to capitalize and amortize U.S. based research development expenses over a period of five years and non-U.S. based research and development expenses over a period of 15 years effective for tax years beginning after December 31, 2021. In assessing the need for a valuation allowance, management must determine that there will be sufficient taxable income to allow for the realization of deferred tax assets. Based upon the historical and anticipated future losses, management has determined that the deferred tax assets do not meet the more likely than not threshold for realizability. Accordingly, a full valuation allowance has been recorded against the Company’s net deferred tax assets as of December 31, 2023 and December 31, 2022. The valuation allowance increased by \$36.6 million and \$35.7 million during the years ended December 31, 2023 and 2022, respectively.

**PRELUDE THERAPEUTICS INCORPORATED**

**NOTES TO FINANCIAL STATEMENTS — Continued**

A reconciliation of the federal income tax rate to the Company’s effective tax rate is as follows:

	Year ended December 31,	
	2023	2022
Federal tax benefit at statutory rate .....	(21.0)%	(21.0)%
State tax, net of federal benefit.....	(6.6)	(6.6)
Permanent differences .....	1.1	0.8
Research and development.....	(4.4)	(3.5)
Change in valuation allowance.....	30.0	30.9
Share-based compensation .....	0.9	-
Other.....	-	(0.6)
	0%	0%

The following table summarizes carryforwards of federal and state net operating losses (“NOL”) and research tax credits:

(in thousands)	December 31,	
	2023	2022
NOL carryforwards - Federal .....	\$ 257,976	\$ 236,898
NOL carryforwards - State .....	259,051	237,565
Research tax credits - Federal.....	20,521	15,201
Research tax credits - State .....	43	43

The NOL carryforwards begin expiring in 2036 for federal and Delaware state income tax purposes, however; all federal, Delaware state, and Kansas state NOL carryforwards generated subsequent to January 1, 2018, are able to be carried forward indefinitely. The NOL carryforwards begin expiring in 2037 and 2042 for Tennessee and Massachusetts, respectively. As of December 31, 2023, the Company also had federal and Delaware research and development tax credit carryforwards of \$20.5 million and \$43 thousand, respectively, that will begin to expire in 2039 and 2031, respectively, unless previously utilized.

The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. To date, the Company has not performed an analysis to determine whether or not ownership changes have occurred since inception. Delaware state NOLs may also be limited.

As of December 31, 2023, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company’s statement of operations. Due to NOL and tax credit carry-forwards that remain unutilized, income tax returns for all tax years remain subject to examination by the taxing jurisdictions. The NOL carryforwards remain subject to review until utilized.

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

None.

**Item 9A. Controls and Procedures.****Evaluation of Disclosure Controls and Procedure**

Under the supervision and with the participation of our management, including our Chief Executive Officer (Our principal executive officer) and our Chief Financial Officer (Our principal accounting officer), we evaluated the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2023. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on our management’s evaluation (with the participation of our Chief Executive Officer and our Chief Financial Officer), as of the end of the period covered by this report, our Chief Executive Officer and our Chief Financial Officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

**Management’s Annual Report on Internal Control Over Financial Reporting**

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness 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. Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external reporting purposes in accordance with U.S. generally accepted accounting principles.

Our management conducted an assessment of our internal control over financial reporting based on the framework established in 2013 by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013). Based on the assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2023.

**Changes in Internal Control over Financial Reporting**

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2023 that have materially affected, or are reasonably likely to materially affect, our internal controls over financial reporting.

**Item 9B. Other Information.**

None.

**Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.**

None.

### **PART III**

#### **Item 10. Directors, Executive Officers and Corporate Governance.**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

#### **Item 11. Executive Compensation**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

#### **Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

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

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

#### **Item 14. Principal Accounting Fees and Services.**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2024 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

## PART IV

### Item 15. Exhibit and Financial Statement Schedules.

(1) *Financial Statements:*

The financial statements required by Item 15(a) are filed as part of this Annual Report on Form 10-K under Item 8 “Financial Statements and Supplementary Data.”

(2) *Financial Statement Schedules*

The financial statement schedules required by Item 15(a) are omitted because they are not applicable, not required or the required information is included in the financial statements or notes thereto as filed in Item 8 of this Annual Report on Form 10-K.

(3) *Exhibits.*

Exhibit Number	Exhibit Title	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
3.1	Restated Certificate of Incorporation of Prelude Therapeutics Incorporated.	10-Q	001-39527	3.1	August 3, 2023	
3.2	Amended and Restated Bylaws of Prelude Therapeutics Incorporated.	8-K	001-39527	3.1	January 23, 2023	
4.1	Form of Common Stock Certificate.	S-1/A	333-248628	4.1	September 16, 2020	
4.2	Amended and Restated Investors’ Rights Agreement, dated August 21, 2020, by and among Prelude Therapeutics Incorporated and certain of its stockholders	S-1/A	333-248628	4.2	September 16, 2020	
4.3	Form of Registration Rights Agreement, by and among Prelude Therapeutics Incorporated and certain of its stockholders.	S-1	333-251874	4.3	January 4, 2021	
4.4	Form of Amended and Restated Registration Rights Agreement by and among Prelude Therapeutics Incorporated and certain Investors.					X
4.5	Description of Voting Common Stock Registered Under Section 12 of the Securities Exchange Act of 1943, as amended.					X
4.6	Form of Pre-Funded Warrant	8-K	001-39527	4.1	May 19, 2023	
4.7	Form of Pre-Funded Warrant	8-K	001-39527	4.1	December 11, 2023	
10.1+	Form of Indemnification Agreement with directors and officers.	S-1	333-248628	10.1	September 4, 2020	
10.2+	2016 Stock Incentive Plan, as amended, and forms of award agreements.	S-1	333-248628	10.2	September 4, 2020	
10.3+	2020 Equity Incentive Plan and forms of award agreements.	S-1/A	333-248628	10.3	September 21, 2020	
10.4+	2020 Employee Stock Purchase Plan and forms of award agreements.	S-1/A	333-248628	10.4	September 21, 2020	
10.5	Second Amended and Restated Entrepreneur Client License Agreement, dated November 1, 2020, by and between Prelude Therapeutics Incorporated and Delaware Innovation Space, Inc.	8-K	001-39527	10.1	November 4, 2020	



Exhibit Number	Exhibit Title	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
10.6+	Executive Employment Agreement, dated December 30, 2020, by and between the Prelude Therapeutics Incorporated and Krishna Vaddi.	S-1	333-251874	10.6	January 4, 2021	
10.7+	Executive Employment Agreement, dated January 30, 2023, by and between the Registrant and Bryant Lim.					X
10.8+	Executive Employment Agreement, dated January 21, 2022, by and between Registrant and Jane Huang.	10-Q	001-39527	10.1	May 10, 2022	
10.9††	Single-Tenant Triple Net Lease, dated November 30, 2021, by and between the Registrant and Crisp Partners, LLC.	10-K	001-39527	10.11	March 17, 2022	
10.10††	First Amendment to Single-Tenant Triple Net Lease, dated November 30, 2021, by and between the Registrant and Crisp Partners, LLC.	10-K	001-39527	10.12	March 17, 2022	
10.11^††	Second Amendment to Single-Tenant Triple Net Lease, dated August 8, 2022, by and between Prelude Therapeutics Incorporated and CRISP Partners LLC.	10-Q	001-39527	10.1	November 14, 2022	
10.12	Open Market Sale Agreement <sup>SM</sup> , dated March 15, 2023, by and between Prelude Therapeutics Incorporated and Jefferies LLC.	8-K	001-39527	1.1	March 15, 2023	
10.13	Form of Securities Purchase Agreement by and among Prelude Therapeutics Incorporated and certain Investors.					X
21.1	Subsidiaries of Prelude Therapeutics Incorporated.					X
23.1	Consent of Ernst and Young LLP, an independent registered public accounting firm.					X
31.1	Certification of Principal Executive 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.					X
31.2	Certification of Principal 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.					X
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
97.1	Compensation Recovery Policy of Prelude Therapeutics Incorporated					X
101.INS	Inline XBRL Instance Document - the instance document does not appear in the Interactive Data File as its XBRL tags are embedded within the Inline XBRL document					X

Exhibit Number	Exhibit Title	Incorporated by Reference				Filed Herewith
		Form	File No.	Exhibit	Filing Date	
101.SCH	Inline XBRL Taxonomy Extension Schema With Embedded Linkbase Documents.					X
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).					X

+ Indicates a management contract or compensatory plan, contract or arrangement.

^ The registrant has omitted portions of the exhibit as permitted under Item 601(b)(10) of Regulation S-K.

†† Certain of the exhibits and schedules to these exhibits have been omitted in accordance with Regulation S-K Item 601(a)(5). The registrant agrees to furnish a copy of all omitted exhibits and schedules to the SEC upon its request.

\* This certification is deemed not filed for purpose of section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

### Item 16. Form 10-K Summary

None.



