Nuvalent

2021 Annual Report

Nasdaq: **NUVL**

DEAR SHAREHOLDERS,

At Nuvalent, we are not just creating the next generation of small molecule kinase inhibitors:

Our focused mission is to discover, develop, and deliver a portfolio of ***"Precisely Targeted Therapies"*** for patients with cancer – novel drug candidates differentiated through intentional kinase selectivity, and purpose-built to overcome the specific limitations of the targeted therapies available to patients today.

At our core is a deep expertise in chemistry and structure-based drug design. We combine this expertise with close collaborative relationships with leading physician-scientists to pursue new molecules that could represent the best possible solution today for each individual oncogenic driver. Our goal, simply, is to drive deeper, more durable responses for patients with cancer.

While kinase inhibitors have historically been developed across multiple biomarker selected populations, we believe patients deserve a new generation of therapies tailor made for the unique set of challenges that they experience due to their tumor's specific biology. By focusing first on clinically proven kinase targets, we are able to build on existing structural and clinical insights, increasing sophistication in research models and clinical trial conduct, and growing regulatory precedent, with the goal of efficiently advancing our novel programs from bench to clinical development, and ultimately to the patients they are specifically designed to benefit.

Throughout 2021 and early 2022, the Nuvalent team has established a strong foundation on which we are building towards multiple near-term opportunities for clinical proof-of-concept.

Our key accomplishments include:

- Anchored our development pipeline with two wholly-owned and internally discovered parallel lead product candidates: NVL-520, a ROS1-selective inhibitor, and NVL-655, an ALK-selective inhibitor
- Advanced both of our parallel lead product candidates into clinical development:
  - NVL-520 is under active clinical investigation in the Phase 1 portion of the Phase 1/2 ARROS-1 study for patients with advanced ROS1-positive NSCLC and other solid tumors
  - The FDA has confirmed that the IND for NVL-655 may proceed. We plan to initiate the Phase 1/2 ALKOVE-1 study of NVL-655 for patients with advanced ALK-positive NSCLC and other solid tumors in the second quarter of 2022.

ARROS-1

ALKOVE-1

- Strengthened our organization, including key appointments to our leadership team and board of directors
  - Appointed Anna Protopapas as Chair of our board of directors. Ms. Protopapas is President and Chief Executive Officer of Mersana Therapeutics, and brings broad industry experience ranging from global development to commercial expertise with a focus on building companies from start-ups to leaders in their categories.
  - Appointed Emily Drabant Conley, PhD as a new independent director. Dr. Conley is Chief Executive Officer of Federation Bio, and brings a unique perspective encompassing the development of both oncology therapeutics as well as cutting-edge diagnostics through her experience in growing 23andMe into a household name.
- Bolstered our balance sheet with the successful completion of our upsized $190.6 million initial public offering in August 2021
- Continued advancement and expansion of our internal discovery pipeline, including two disclosed programs for patients with HER2 Exon 20 insertions and ALK IXDN compound mutations

With the expected drug candidate nominations in 2022 for our HER2 Exon 20 and ALK IXDN programs, our team has the potential to deliver four development candidate nominations within four years – a testament to both the strength and efficiency of our team and approach.

As we look to the rest of 2022, our strategic priorities remain on focused, capital efficient execution towards clinical proof-of-concept and pipeline expansion. We are continually inspired and humbled by the patients, their families, and caregivers who remind us daily why we do what we do. It is for these brave and passionate individuals that we are steadfast in our aim of bringing a new generation of *Precisely* Targeted Therapies to patients with cancer.

In closing, I would like to extend my gratitude to the Nuvalent team, our collaborators, and our investors for their unwavering resolve to prioritize patient benefit and nurture a community that we are each proud to be a part of. I strongly believe that together, we have a promising future ahead.

James R. Porter Ph.D. | Chief Executive Officer

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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021

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: 001-40671

NUVALENT, INC.

(Exact name of registrant as specified in its charter)

Delaware	**83-5112298**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
One Broadway, 14th Floor Cambridge, MA	**02142**
(Address of principal executive offices)	**(Zip Code)**

(857) 357-7000

(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Class A Common Stock, $0.0001 Par Value	NUVL	Nasdaq Global Select Market

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

None

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

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

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

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 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, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

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

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

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

As of June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, there was no established public market for the registrant's Class A common stock. The registrant therefore cannot calculate the aggregate market value of its voting and non-voting common equity held by non-affiliates as of such date. The registrant's Class A common stock began trading on The Nasdaq Global Select Market on July 29, 2021.

As of February 28, 2022, there were 42,878,747 shares of the registrant's Class A Common Stock, $0.0001 par value per share, outstanding and 5,435,254 shares of the registrant's Class B Common Stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Proxy Statement for its 2022 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Nuvalent, Inc.
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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K (Annual Report) of Nuvalent, Inc. contains express or implied forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act), that are based on our management's belief and assumptions and on information currently available to our management. These statements relate to future events or our future operational or financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements contained in this Annual Report include, among other things, statements about:

- the initiation, timing, progress, results, and cost of NVL-520 and NVL-655, as well as our discovery programs and our current and future preclinical and clinical studies, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our current and future programs;
- the ability of our preclinical studies and clinical trials to demonstrate safety and efficacy of our product candidates, and other positive results;
- the beneficial characteristics, and the potential safety, efficacy and therapeutic effects of our product candidates;
- the timing, scope and likelihood of regulatory filings and approvals, including timing of Investigational New Drug applications (INDs) and final U.S. Food and Drug Administration (FDA) approval of our current product candidates or any future product candidates;
- the timing, scope or likelihood of foreign regulatory filings and approvals;
- our ability to identify research priorities and apply a risk-mitigated strategy to efficiently discover and develop product candidates, including by applying learnings from one program to other programs and from one indication to our other indications;
- our estimates of the number of patients that we will enroll and our ability to initiate, recruit, and enroll patients in and conduct and successfully complete our clinical trials at the pace that we project;
- our ability to scale-up our manufacturing and processing approaches to appropriately address our anticipated commercial needs, which will require significant resources;
- our ability to maintain and further develop the specific shipping, storage, handling and administration of NVL-520 and NVL-655 at the clinical sites;
- our ability to obtain funding for our operations necessary to complete further development and commercialization of our product candidates;
- our ability to take advantage of accelerated regulatory pathways for our product candidates;
- our ability to obtain and maintain regulatory approval of our product candidates;
- our ability to commercialize our product candidates, if approved, including the geographic areas of focus and sales strategy;
- the pricing and reimbursement of our product candidates, if approved;
- the implementation of our business model, and strategic plans for our business, product candidates, and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and other product candidates we may develop, including the extensions of existing patent terms where available, the validity of intellectual property rights held by third parties, and our ability not to infringe, misappropriate or otherwise violate any third-party intellectual property rights;

- estimates of our future expenses, revenues, capital requirements, and our needs for additional financing;
- the period over which we estimate our existing cash, cash equivalents and marketable securities will be sufficient to fund our future operating expenses and capital expenditure requirements;
- future agreements with third parties in connection with the development and commercialization of our product candidates;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- our financial performance;
- the rate and degree of market acceptance of our product candidates;
- regulatory developments in the United States (the U.S.) and foreign countries;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our ability to produce our product candidates with advantages in turnaround times or manufacturing cost;
- our competitive position and the success of competing therapies that are or may become available;
- our need for and ability to attract and retain key scientific, management and other personnel;
- the impact of laws and regulations;
- our expectations regarding the period during which we will remain an emerging growth company under the Jumpstart Our Business Startups Act of 2012 (the JOBS Act);
- developments relating to our competitors and our industry;
- the effect of the COVID-19 pandemic, including mitigation efforts and economic effects, on any of the foregoing or other aspects of our business operations, including but not limited to our preclinical studies and future clinical trials; and
- other risks and uncertainties, including those listed under the section titled “Risk Factors.”

In some cases, you can identify forward-looking statements by terminology such as “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “expect,” “estimate,” “seek,” “predict,” “future,” “project,” “potential,” “continue,” “target” or the negative of these terms or other comparable terminology. These statements are only predictions. You should not place undue reliance on forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, which are, in some cases, beyond our control and which could materially affect results. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under the section titled “Risk Factors” and elsewhere in this Annual Report. If one or more of these risks or uncertainties were to occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those implied or projected by the forward-looking statements. No forward-looking statement is a guarantee of future performance. You should read this Annual Report and the documents that we reference in this Annual Report and have filed with the Securities and Exchange Commission (the SEC) thereto completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements.

The forward-looking statements in this Annual Report represent our views as of the date of this Annual Report. We do not undertake any obligation to publicly update any forward-looking statement except to the extent required by applicable law. You should therefore not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this Annual Report.

This Annual Report also contains estimates, projections and other information concerning our industry, our business and the markets for our product candidates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless

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

Except where the context otherwise requires or where otherwise indicated, the terms “Nuvalent,” “we,” “us,” “our,” “our company,” “the company,” and “our business” in this Annual Report refer to Nuvalent, Inc. and its consolidated subsidiary.

SUMMARY OF RISK FACTORS

Below is a summary of the principal factors that make an investment in our common stock speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the section titled "Risk Factors" and should be carefully considered, together with other information in this Annual Report and our other filings with the SEC before making investment decisions regarding our common stock.

- We are very early in our development efforts, have a limited operating history, have not completed any clinical trials, have no products approved for commercial sale and have not generated any revenue, which may make it difficult for investors to evaluate our current business and likelihood of success and viability;
- We have incurred significant net losses in each period since our inception, and we expect to continue to incur significant net losses for the foreseeable future;
- We are very early in our development efforts and our future prospects are substantially dependent on NVL-520 and NVL-655;
- Our preclinical studies and clinical trials may fail to adequately demonstrate the safety and efficacy of any of our product candidates, which would prevent or delay development, regulatory approval and commercialization;
- Our discovery and preclinical development activities are focused on the development of targeted therapeutics for patients with cancer-associated genomic alterations, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs may never lead to approved or marketable products;
- In addition to NVL-520 and NVL-655, our prospects depend in part upon discovering, developing and commercializing additional product candidates from our ALK IXDN, HER2 and other discovery programs, which may fail in development or suffer delays that adversely affect their commercial viability;
- Our approach to the discovery and development of product candidates is unproven, and we may not be successful in our efforts to use and expand our approach to build a pipeline of product candidates with commercial value;
- We may not be able to submit INDs, clinical trial applications (CTAs) or comparable applications to commence clinical trials on the timelines we expect, and even if we are able to, regulatory authorities may not permit us to proceed;
- Our product candidates may cause undesirable adverse events when used alone or in combination with other products that may result in a safety profile that could prevent regulatory approval, prevent market acceptance, limit their commercial potential or result in significant negative consequences;
- If we experience delays or difficulties in the enrollment or maintenance of patients in clinical trials, our regulatory submissions or receipt of necessary marketing approvals could be delayed or prevented;
- The effects of the ongoing COVID-19 pandemic could adversely impact our business, including our clinical trials and preclinical studies;
- We face substantial competition which may result in others discovering, developing or commercializing products before or more successfully than we do;
- If any of our third-party manufacturers encounter difficulties in production, our ability to provide adequate supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or prevented;
- The market opportunities for any product candidates we develop, if approved, may be limited to certain smaller patient subsets and may be smaller than we estimate them to be;
- We may be unable to obtain U.S. or foreign regulatory approval and, as a result, may be unable to commercialize our product candidates;

- We have never commercialized a product candidate as a company before and currently lack the necessary expertise, personnel and resources to successfully commercialize any products on our own or together with suitable collaborators;
- Even if our product candidates receive regulatory approval, they will be subject to significant post-marketing regulatory requirements and oversight;
- Where appropriate, we plan to secure approval through the use of accelerated registration pathways. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we are currently contemplating, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals;
- Our relationships with healthcare professionals, clinical investigators, contract research organizations (CROs) and third-party payors in connection with our current and future business activities may be subject to federal and state healthcare fraud and abuse laws, false claims laws, transparency laws, government price reporting, and health information privacy and security laws, which could expose us to significant losses;
- Our reliance on a limited number of employees who provide various administrative, research and development, and other services across our organization presents operational challenges that may adversely affect our business;
- If we are unable to establish sales or marketing capabilities or enter into agreements with third parties to sell or market our product candidates, we may not be able to successfully sell or market our product candidates that obtain regulatory approval;
- If we are unable to obtain, maintain and enforce patent protection for our technology and product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully develop and commercialize our technology and product candidates may be adversely affected;
- We may become involved in lawsuits to protect or enforce our patent or other intellectual property rights, which could be expensive, time-consuming and unsuccessful;
- Third parties may allege that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on our business;
- If we are unable to protect the confidentiality of our trade secrets and other proprietary information, our business and competitive position would be adversely affected;
- If our trademarks and trade names are not adequately protected, we may not be able to build name recognition in our markets of interest and our business may be adversely affected;
- We rely on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research and studies;
- If we decide to establish collaborations, but are not able to establish those collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans;
- Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance;
- Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval. Three of our directors are affiliated with our principal stockholders; and
- We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

PART I

ITEM 1. BUSINESS

Overview

We are a clinical stage biopharmaceutical company focused on creating *precisely* targeted therapies for patients with cancer. We leverage our team's deep expertise in chemistry and structure-based drug design to develop innovative small molecules that are designed with the aim to overcome the limitations of existing therapies for clinically proven kinase targets. Through addressing the limitations of existing therapies, we believe our programs have the potential to drive deeper, more durable responses with minimal adverse events. We believe these potential benefits will support opportunities for clinical utility earlier in the treatment paradigm.

We focus our discovery efforts on small molecule inhibitors of kinases, a class of cellular targets that can play a central role in cancer growth and proliferation. In particular, we focus on "clinically proven" kinase targets, or those for which therapies have been developed by others to target those kinases, and that such drugs have demonstrated sufficient clinical efficacy and safety data to be approved by the FDA or similar regulatory agency and are established and used in the clinical setting. Currently available kinase inhibitors face multiple limitations, which can include kinase resistance, or the emergence of new mutations in the kinase target that can enable resistance to existing therapies; kinase selectivity, or the potential for existing therapies to inhibit other structurally similar kinase targets and lead to off-target adverse events; and limited brain penetrance, or the ability for the therapy to treat disease that has spread or metastasized to the brain. By prioritizing target selectivity, we believe our drug candidates have the potential to overcome resistance, minimize adverse events, optimize brain penetrance to address brain metastases, and drive more durable responses.

We are advancing a robust pipeline of product candidates with parallel lead programs in cancers driven by genomic alterations in the ROS proto-oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) kinases (*i.e.,* ROS1-positive and ALK-positive, respectively), along with multiple discovery-stage research programs. We hold worldwide development and commercialization rights to our product candidates.

Our first lead product candidate, NVL-520, is a novel ROS1-selective inhibitor designed with the aim to address the clinical challenges of emergent treatment resistance, central nervous system (CNS)-related adverse events, and brain metastases that may limit the use of currently available ROS1 tyrosine kinase inhibitors (TKI). Preclinical data has shown that NVL-520 was brain-penetrant, inhibited wild-type ROS1 fusions, remained active in the presence of mutations conferring resistance to approved and investigational ROS1 inhibitors, and displayed strong selectivity for both wild-type ROS1 and its resistance variants as compared to the structurally related tropomyosin receptor kinase B (TRKB), thereby minimizing the potential for off-target TRKB-related CNS adverse events.

We are currently enrolling patients in the Phase 1 portion of our ARROS-1 clinical trial, a first-in-human Phase 1/2, multicenter, open-label, dose-escalation and expansion study evaluating NVL-520 as an oral monotherapy in patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other solid tumors. ARROS-1 is comprised of two study components, beginning with a Phase 1 dose-escalation portion to evaluate the safety and tolerability of NVL-520 in patients with advanced ROS1-positive solid tumors previously treated with at least one ROS1 TKI, as well as to determine the recommended Phase 2 dose (RP2D), characterize the pharmacokinetic profile, and evaluate preliminary anti-tumor activity of NVL-520. Once the RP2D is determined, the study may transition directly into a Phase 2 portion designed to support potential registration of NVL-520 in both ROS1-positive patients with NSCLC who are TKI-naïve and who have been previously treated with ROS1 kinase inhibitors.

Our second lead product candidate, NVL-655, is a brain-penetrant ALK-selective inhibitor, designed with the aim to address the clinical challenges of emergent treatment resistance, CNS-related adverse events, and brain metastases that may limit the use of first-, second-, and third-generation ALK inhibitors. Preclinical data has shown that NVL-655 was brain-penetrant, inhibited wild-type ALK fusions, remained active in the presence of mutations conferring resistance to approved and investigational ALK inhibitors, and displayed strong selectivity

for both wild-type ALK and its resistance variants as compared to the structurally related TRKB, thereby minimizing the potential for off-target TRKB-related CNS adverse events. We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the Phase 1 portion of our planned ALKOVE-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022.

In addition to our lead programs, we have prioritized a number of additional small molecule research programs following an assessment of medical need, including a second ALK inhibitor program designed with the aim to address emerging compound resistance mutations and a HER2 Exon 20 insertions program. We expect to nominate product candidates for these programs in 2022.

Within the past decade, the increase in the utilization of cancer genomic profiling has resulted in the identification of specific genomic alterations, such as ROS1 fusions and ALK fusions, that can drive the growth and proliferation of a tumor. The successful development of targeted therapies matched to individual genomic alterations has given rise to the current era of precision oncology, where treatment decisions driven by the genomic profile of a patient's cancer are increasingly becoming the standard of care.

In particular, kinase inhibitors have fueled the targeted therapy revolution and remain at the leading edge of precision oncology. However, the clinical utility of currently approved kinase inhibitors is limited by three key challenges: kinase resistance, kinase selectivity, and, for some tumor types, limited CNS activity.

Our approach is to create innovative molecular structures and nominate product candidates that have the potential to overcome the limitations of existing therapies for clinically proven kinase targets. Our structures are designed to precisely engage the target kinase and remain active in tumors that have developed resistance, enabling our product candidates to treat both the original tumor and tumors with emergent resistance mutations. In addition, we prioritize structures that are highly selective for their target kinases in order to minimize adverse events and drive durable responses. Where appropriate, we optimize for brain penetrance to improve treatment options for patients with brain metastases.

By addressing the limitations of existing therapies, we believe our programs have the potential to drive deeper, more durable responses with minimal adverse events. We believe these potential benefits will support opportunities for clinical utility earlier in the treatment paradigm.

Our approach

Our approach is built on three core principles:

- ***Patient-driven focus.*** We prioritize therapeutic targets where patient needs and limitations of existing therapies can be identified and characterized in partnership with physician-scientists. Leveraging our team's deep expertise and experience in drug discovery, we translate those medical insights into detailed target product profiles with well-defined selection criteria to ensure that our product candidates are purpose-built to address specific and current medical needs.
- ***Deep expertise in chemistry and structure-based drug design to achieve precise selectivity ("Threading the needle").*** We prioritize exquisite target selectivity in the design of our molecules to precisely meet the selection criteria we have pre-defined in our target product profiles. Leveraging our team's deep expertise in chemistry and structure-based drug design, we 'thread the needle' to navigate competing molecular challenges and develop innovative small molecules that have the potential to overcome resistance, minimize adverse events, optimize CNS activity, and drive more durable responses.
- ***Efficient drug discovery and development.*** We prioritize programs that may leverage our pipeline discovery and development efforts and experience, with a specific focus on clinically proven kinase targets, with the goal of bringing our therapies to patients as soon as possible. Building on existing discovery tools and processes for the investigation of clinically proven kinase targets, we further leverage our team's deep experience in the advancement of oncology product candidates from nomination through clinical development, as well as potential opportunities for accelerated regulatory pathways, to achieve an efficient approach to drug discovery and development.

Our approach has enabled us to identify two product candidates in two years, and we expect to nominate two more product candidates in 2022. With the continued increase in the adoption of kinase inhibitors as the standard of care across a broadening set of indications, we believe that opportunities to apply our established approach of efficient drug discovery and development will continue to grow.

Our programs

We are currently advancing two parallel lead programs in addition to multiple early-stage discovery programs as summarized in Figure 1 below. We hold worldwide development and commercialization rights to our product candidates.

Figure 1. Our pipeline of kinase inhibitor product candidates

NVL-520 (ROS1-Selective inhibitor)

The ROS1 kinase is a clinically proven target in oncology, with two therapies that target the ROS1 kinase that have received FDA marketing approval for the treatment of ROS1-positive NSCLC: Xalkori® (crizotinib), a dual ROS1/ALK inhibitor marketed by Pfizer Inc. (Pfizer); and Rozlytrek® (entrectinib), a dual ROS1/TRK inhibitor marketed by F. Hoffmann-La Roche AG (Roche) and its partners. We believe NVL-520 is a differentiated product candidate for patients with advanced NSCLC driven by a ROS1 fusion (*i.e.,* ROS1-positive). NVL-520 is a brain-penetrant ROS1-selective inhibitor designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with the prevalent G2032R resistance mutation and those with the S1986Y/F, L2026M, or D2033N resistance mutations. We optimized NVL-520 for brain penetrance to potentially improve treatment options for patients with brain metastases. Importantly, we observed that NVL-520 selectively inhibits ROS1 over the structurally related tropomyosin receptor kinase (TRK) family to potentially avoid TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1-mutant variants. The Phase 1 portion of our ARROS-1 study, a Phase 1/2 clinical trial investigating NVL-520 in advanced ROS1-positive NSCLC and other solid tumors, is open and enrolling.

NVL-655 (ALK-Selective inhibitor)

The ALK kinase is a clinically proven target in oncology, with five therapies that target the ALK kinase that have received FDA marketing approval for the treatment of ALK-positive NSCLC: Xalkori (crizotinib) and Lorbrena®

(lorlatinib), each marketed by Pfizer; Zykadia® (ceritinib), marketed by Novartis AG (Novartis); Alecensa® (alectinib), marketed by Roche and Chugai Pharmaceutical Co., Ltd. (Chugai); and Alunbrig® (brigatinib), marketed by Takeda Pharmaceutical Company Limited (Takeda). We believe NVL-655 is a differentiated product candidate for patients with advanced NSCLC driven by an ALK fusion (*i.e.*, ALK-positive). NVL-655 is a brain-penetrant ALK-selective inhibitor designed with the aim to remain active in tumors that have developed resistance to first-, second-, and third-generation ALK inhibitors, including tumors with the G1202R resistance mutation or compound resistance mutations G1202R/L1196M (GRLM), G1202R/G1269A (GRGA), or G1202R/L1198F (GRLF and, together with GRLM and GRGA, referred to as G1202R+). We believe we have optimized NVL-655 for brain penetrance and ALK selectivity to potentially improve treatment options for patients with brain metastases and avoid CNS adverse events related to off-target inhibition of the structurally related TRK family. We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the Phase 1 portion of our planned ALKOVE-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022.

Discovery programs

In addition to our lead programs, we have prioritized a number of additional small molecule research programs following assessment of medical need, including a second ALK inhibitor program designed with the aim to address emerging compound resistance mutations and a HER2 Exon 20 insertions program. Our key discovery programs are summarized below:

ALK IXDN

The ALK I1171X (X = N, S, or T) / D1203N (IXDN) compound mutations are emerging mutations that confer resistance to all available ALK inhibitor therapies for NSCLC. For patients treated with current first-line standard of care alectinib, the most prevalent ALK drug-resistance mutations are G1202R and I1171X. Following second-line treatment with lorlatinib, IXDN compound mutations have been observed. There are no approved therapies for the treatment of NSCLC with IXDN compound mutations. We are advancing toward a novel, selective, brain-penetrant ALK inhibitor designed with the aim to remain active in tumors harboring IXDN compound resistance mutations. We expect to nominate a product candidate in 2022.

HER2 Exon 20 insertions

Mutations in human epidermal growth factor receptor 2 (HER2 or ERBB2) occur in up to 4% of metastatic NSCLCs, with in-frame deletions, insertions, or duplications in exon 20 accounting for 90% of cases (collectively, HER2 Exon 20 Insertions). Approximately 20% of patients with HER2 mutant NSCLC present with brain metastases, with the percentage increasing upon treatment. There are no approved targeted therapies for NSCLC patients with HER2 Exon 20 Insertions. We are advancing toward a novel, selective, brain-penetrant HER2 inhibitor to treat patients with HER2 Exon 20 Insertions, including those with brain metastases, and to minimize adverse events and dose-limiting toxicities related to off-target inhibition of HER2 family member epidermal growth factor receptor (EGFR). We expect to nominate a product candidate in 2022.

Our team

We have assembled a management team of biopharmaceutical industry veterans with extensive experience in developing novel oncology therapies from research through commercialization. Our team is led by our Chief Executive Officer, James R. Porter, Ph.D., who has over 20 years of experience, including at Infinity Pharmaceuticals, Inc. (Infinity) and Verastem Oncology. Our Chief Financial Officer, Alexandra Balcom, M.B.A., C.P.A., has over 16 years of industry experience and was previously at SQZ Biotechnologies Company and Agios Pharmaceuticals, Inc. Our Chief Medical Officer, Christopher D. Turner, M.D., has over 20 years of experience in drug development, including at ARIAD Pharmaceuticals, Inc. and Blueprint Medicines Corporation. Our Chief Legal Officer, Deborah Miller, Ph.D., J.D., has over 20 years of legal experience managing the entire pharmaceutical lifecycle from early discovery through litigation, including at Sumitomo Dainippon Pharma America, Inc. and Infinity. Our Senior Vice President of Product Development & Regulatory

Affairs, Darlene Noci, A.L.M., has over 20 years of experience in global drug development in rare diseases and oncology, including at Genzyme Corporation and EMD Serono, the North America biopharma business of Merck KgaA, Darmstadt, Germany.

Our seasoned leadership team has broad experience at both large global organizations, including C.H. Boehringer Sohn AG & Ko. KG, Pfizer, Sanofi S.A., EMD Serono, GlaxoSmithKline plc, and BeiGene, Ltd., as well as established biotech companies, including Infinity, Agios Pharmaceuticals Inc., Blueprint Medicines Corporation, and ARIAD Pharmaceuticals, Inc. Together, our leadership team has contributed directly to the regulatory approval of 12 therapies, including 5 kinase inhibitors, 9 oncology therapeutics, and 10 small molecules: CLOLAR®/Evoltra® (clofarabine), FABRAZYME® (agalsidase beta), COPIKTRA® (duvelisib), BRUKINSA® (zanubrutinib), MOZOBIL® (plerixafor injection), BAVENCIO® (avelumab), TIBSOVO® (ivosidenib tablets), TIVICAY® (dolutegravir), ICLUSIG® (ponatinib), GAVRETO™ (pralsetinib), ALUNBRIG® (brigatinib) and PYRUKYND® (mitapivat).

Our discovery approach leverages the experience and ongoing support of our scientific founder and head scientific advisor Matthew Shair, Ph.D., Professor of Chemistry and Chemical Biology at Harvard University. In leading his laboratory at Harvard, Dr. Shair has integrated organic chemistry, human disease biology, and drug development to focus on the development of novel small molecule therapeutics, and he has developed ways to efficiently assemble complex small molecules.

Our scientific advisors include additional researchers who publish widely cited research on topics relevant to the study and treatment of cancer, lead clinical units at experienced precision medicine cancer centers in the U.S., and are actively involved in our drug development process and programs. Our strong scientific advisory board includes:

- Matthew Shair, Ph.D., head scientific advisor, Professor of Chemistry and Chemical Biology at Harvard University. Dr. Shair is the scientific founder of Nuvalent and is on our board of directors;
- Michael Meyers, M.D., Ph.D., clinical advisor, Chief Medical Officer at Syndax;
- Pasi Jänne, M.D., Ph.D., clinical advisor, Dana Farber Cancer Institute;
- Ross Camidge, M.D., Ph.D., clinical advisor, Professor at University of Colorado;
- Alexander Drilon, M.D., clinical advisor, Memorial Sloan Kettering;
- Aaron Hata, M.D., Ph.D., translational research advisor, Massachusetts General Hospital; and
- Nancy Kohl, Ph.D., translational research advisor, independent consultant.

We have also established collaborations through service agreements with global CROs to provide scale and expertise in research chemistry, chemical manufacturing, biology, pharmacology and toxicology, and clinical studies.

Our values

Our three core values are:

- ***Patient Impact***. We care deeply about what we are building to change the future for patients.
- ***Empowerment***. We are all responsible for delivering on our mission to develop new medicines for patients: listen, speak up, engage.
- ***Collaboration***. We know that we are better together and thrive when we challenge each other to find a better way for patients.

Our strategy

Our goal is to be a leading biopharmaceutical company that translates our deep expertise in structure-based drug design to discover, develop, and deliver novel, selective therapeutics that enable durable responses for patients with cancer. The key elements of our strategy include:

- ***Advance the ongoing clinical development of NVL-520, our first lead product candidate and a differentiated ROS1-selective inhibitor, in the Phase 1/2 ARROS-1 study designed to support potential regulatory approval.*** We believe that NVL-520 is positioned to be a differentiated inhibitor of ROS1 based on its activity against wild-type ROS1 fusions and key resistance mutations, selectivity over other kinases associated with adverse events and dose-limiting toxicities, and activity in the CNS to address brain metastases. We believe that these characteristics may position NVL-520 to deliver a favorable tolerability profile and more robust anti-tumor response than existing ROS1 inhibitors, which has the potential to drive more durable responses in patients. Clinical investigation of NVL-520 is ongoing in the Phase 1 portion of our ARROS-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-520 in advanced ROS1-positive NSCLC and other solid tumors. Pending supportive data, we plan to engage with regulators to discuss whether we may qualify for any expedited drug development pathways.
- ***Advance NVL-655, our second lead product candidate, a differentiated ALK-selective inhibitor, through clinical development and regulatory approval.*** We designed NVL-655 to have a compelling product profile with activity against wild-type ALK fusions and drug-resistant mutations in ALK-driven tumors, selectivity over other kinases associated with adverse events and dose-limiting toxicities, and activity in the CNS to address brain metastases. We believe that these characteristics position NVL-655 to be a differentiated ALK inhibitor that may deliver a favorable tolerability profile and more robust anti-tumor response than existing therapies. We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the Phase 1 portion of our planned ALKOVE-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022. Pending supportive data, we plan to engage with regulators to discuss whether we may qualify for any expedited drug development pathways.
- ***Continue to partner with physician-scientists to characterize current and emerging medical needs for patients and the limitations of existing therapies.*** We prioritize clinically proven kinase targets where clear remaining or emerging medical needs for patients can be defined by our physician-scientist partners, and where we believe those needs can be addressed through the design of a highly selective small molecule inhibitor. Combining clinical insight with our drug design capabilities and our development expertise, we seek to meet real-world medical needs through the development of detailed product profiles and well-defined selection criteria. We believe this approach maximizes our opportunity to address the challenges of existing therapies and develop molecules that achieve deep, durable responses with minimal adverse events.
- ***Progress our discovery stage programs, ALK IXDN and HER2 Exon 20 Insertions, while continuing to expand our pipeline of precisely targeted novel product candidates.*** Our approach has enabled us to identify two product candidates in two years, and we expect to nominate two more product candidates in 2022. We prioritize clinically proven kinase targets where the design of exquisitely selective inhibitors may overcome challenges of existing therapies including kinase resistance, kinase selectivity, and limited CNS activity. We have identified a number of additional small molecule research programs following assessment of medical need, including a second ALK inhibitor program designed with the aim to address emerging compound resistance mutations and a program for HER2 Exon 20 Insertions. We intend to develop product candidates as monotherapy treatment and may also strategically pursue the development of synergistic combinations.
- ***Commercialize our product candidates in key geographies and opportunistically pursue strategic collaborations to maximize the full potential of our pipeline.*** We retain full development and worldwide commercialization rights to our pipeline of *precisely* targeted therapies. We intend to build a fully integrated biopharmaceutical company and independently pursue the development and commercialization of our key product candidates, if approved. In the future, we may enter into strategic collaborations around certain

targets, product candidates, disease areas, or geographies, if we believe these collaborations could accelerate the development and commercialization of our product candidates and allow us to realize the full potential of our pipeline.

Background

Cancer is a group of diverse diseases defined by aberrant cell growth and proliferation of abnormal cells. The initiation of cancer can occur when the tightly regulated balance of healthy cell homeostasis is disrupted through a variety of mechanisms, including genomic alterations that lead to dysregulation of key cellular functions.

Historically, cancers were classified by their tissue of origin and stage of clinical progression. However, the advent and increasing adoption of genomic profiling for tumors has enabled expansion of this classification to include recognition of the different molecular origins of cancer. We now understand that tumors, even those arising at different sites throughout the body, often bear genomic alterations in a recurring subset of cancer-associated genes, referred to collectively as oncogenes, that often express signaling proteins for cell proliferation and survival. Furthermore, a subset of these genomic alterations that affect oncogenes appear to be critical drivers of cancer initiation and growth and are therefore referred to as driver alterations. The ability to identify driver alterations within a tumor and the successful development of targeted therapies against them has given rise to the current era of precision oncology, where treatment decisions driven by the genomic profile of a patient's cancer are increasingly becoming the standard of care.

The genes encoding for kinases represent a key category of oncogenes in which driver alterations have been identified and successfully targeted. Kinases are enzymes that regulate the biological activity of proteins, including critical cellular functions such as metabolism, cell cycle regulation, survival, and differentiation, and are subcategorized by the protein residue on which they act (*e.g.,* tyrosine, serine, or threonine). Genomic alterations impacting kinase function can be oncogenic, as dysregulation of key cellular functions can cause normal cells to transform to cancer cells. Cancer cells can be highly dependent on these oncogenic kinase alterations for survival, a concept known as oncogene addiction. As a result, in tumors where an oncogenic driver alteration in a kinase oncogene can be identified, kinase inhibition is a rational and proven approach to disrupt oncogene addiction and lead to arrested cellular growth and proliferation in a targeted manner.

Since the FDA approval of the first targeted kinase inhibitor in 2001, there has been exponential focus on the development of kinase inhibitors for the treatment for cancer. As of January 31, 2022, there were 74 kinase inhibitors approved by the FDA to treat patients with cancer and 34 of these approvals have occurred since 2017. The majority of the currently approved kinase inhibitors are small molecules that target tyrosine kinases and are referred to as TKIs. The success of TKIs and other kinase inhibitors in oncology is driven by observed clinical benefit, as many patients with tumors driven by oncogenic kinases have demonstrated rapid and measurable tumor shrinkage when treated with a corresponding targeted kinase inhibitor. As a result of their clinical impact, the worldwide sales of small molecule kinase inhibitors in oncology were reported to be $40 billion in 2020 and are estimated to grow to more than $80 billion by 2026.

Limitations of kinase inhibitors

Kinase inhibitors have fueled the targeted therapy revolution and remain at the leading edge of precision oncology. Although advancements in precision oncology have improved outcomes for patients, many patients who initially respond to kinase inhibitors develop resistance to treatment, experience treatment-limiting adverse events, or develop brain metastases that may not be controlled by their initial therapy. This highlights the opportunity for better genomically-driven therapeutics that can overcome kinase resistance, improve kinase selectivity, and, for some tumor types, improve activity in the CNS.

The kinase resistance problem

A common feature of a cancer cell is its ability to gain new mutations in order to sustain its continuous oncogenic signaling and fuel its growth and proliferation. While treatment with currently available kinase inhibitors may provide an initial therapeutic effect, it often results in the emergence of cancer cells harboring new mutations in the kinase target. These new mutations can change the shape and the chemical properties of the kinase binding

pocket, resulting in resistance to therapy. For example, "solvent-front" mutations occur in the solvent-exposed region of the kinase binding pocket where an inhibitor is traditionally designed to fit. Mutations in this solvent-exposed region often cause physical changes to the pocket that disrupt the ability of the kinase inhibitor to bind to its target, leading to the loss of response to the therapy and disease progression. A majority of patients with advanced or metastatic cancer who initially respond to targeted therapies are estimated to eventually develop acquired resistance.

Compounds that are designed to address known resistance mutations to currently approved kinase inhibitors could lead to more durable responses and advance earlier in the treatment paradigm. As an example, the EGFR inhibitor Tagrisso® (osimertinib) was originally developed to treat NSCLC patients that have progressed on first generation inhibitors Iressa® (gefitinib) or Tarceva® (erlotinib) and have developed EGFR T790M, a resistance mutation. Osimertinib was subsequently compared to gefitinib or erlotinib in first-line EGFR NSCLC and demonstrated a statistically significant improvement in progression free survival, attributed in part to preventing the emergence of the EGFR T790M resistance mutation. Today, osimertinib has supplanted the first-generation kinase inhibitors as the standard of care for this patient population. Likewise, the BCR-ABL inhibitor Tasigna® (nilotinib) was initially approved for the treatment of patients with chronic myelogenous leukemia (CML) who were resistant or intolerant to the first-generation inhibitor Gleevec® (imatinib) and was subsequently approved for the treatment of newly diagnosed patients.

The kinase selectivity problem

The drug binding sites of different kinases are often very similar in structure, making it challenging to design molecules that uniquely inhibit a single specific target at therapeutic doses. The similarities between kinases often leads to off-target inhibition, which may contribute to adverse events, dose-limiting toxicities, and insufficient on-target inhibition, ultimately decreasing the duration of clinical response.

Compounds that are designed with greater selectivity could improve tolerability, lead to more durable responses, and advance earlier in the treatment paradigm. As an example, in separate clinical trials, the RET-selective inhibitor Retevmo® (selpercatinib) demonstrated more than twice the response rate and median duration of response in a RET fusion-positive NSCLC patient population compared to the investigational multi-kinase inhibitor, cabozantinib. In another example, clinical adoption of the multi-kinase inhibitor Iclusig® (ponatinib) for CML patients is limited due to off-target vascular adverse events. Ponatinib is not recommended for first-line use despite demonstrating activity against the BCR-ABL T315I mutation that confers resistance to all first-line agents, including Gleevec® (imatinib). This highlights the importance of addressing both kinase resistance and kinase selectivity in parallel to maximize potential opportunities for more durable responses and to advance earlier in the treatment paradigm.

The brain penetration problem

Patients with oncogenic alterations in kinases often present with or develop brain metastases. Approximately 200,000 brain metastases are diagnosed annually in the U.S., accounting for 20% of cancer deaths. Across tumor types, lung cancers and breast cancers constitute the majority of brain metastases. Among lung cancer patients with brain metastases, up to 25% of patients exhibit brain metastases at diagnosis, up to another 50% during the course of disease, and even more at the time of autopsy. Overall, patients presenting with metastatic brain cancer have a poor prognosis with median survival of approximately two months, which may be due to the poor blood-brain barrier (BBB) permeability of currently available therapies.

The growing incidence and unfavorable prognosis of patients with brain metastases highlight the need for therapies that penetrate the BBB to control or prevent disease in the brain. To address the needs of patients presenting with or at risk of developing brain metastases, drug designs must be optimized for structural and physical properties that allow passage through the BBB while also meeting the challenges of kinase resistance to ensure target engagement in the brain, and kinase selectivity to avoid off-target CNS adverse events.

Our approach

We aim to create *precisely* targeted therapies for patients with cancer, designed to overcome the limitations of existing therapies for clinically proven kinase targets. By addressing the limitations of existing therapies, we

believe our programs have the potential to drive deeper, more durable responses with minimal adverse events. These potential benefits may also support opportunities for clinical utility earlier in the treatment paradigm.

As discussed below, our approach is built on three core principles:

- ***Patient-driven focus.***
- ***Deep expertise in chemistry and structure-based drug design to achieve precise selectivity ("Threading the needle").***
- ***Efficient drug discovery and development.***

Our approach has enabled us to identify two product candidates in two years, and we expect to nominate two more product candidates in 2022. With the continued increase in the adoption of kinase inhibitors as the standard of care across a broadening set of indications, we believe that opportunities to apply our established approach to efficient drug discovery and development will continue to grow.

Patient-driven focus

Our goal is to benefit patients, and that is where our process begins. We partner with physician-scientists to assess current and emerging patient needs across potential therapeutic targets. We prioritize clinically proven kinase targets where we believe those needs can be addressed through the design of a highly selective small molecule kinase inhibitor.

Through the combination of clinical insights and our internal drug design and development expertise, we anchor each development program with a detailed target product profile that includes well-defined selection criteria informed by real-world medical needs. Key recurring challenges informing our target product profiles include kinase resistance, kinase selectivity, and limited CNS activity. By aligning with our physician-scientist partners on both the medical needs and target product profile from the beginning, we believe we are able to clearly define the criteria required for molecules that may achieve deep, durable responses with minimal adverse events for patients.

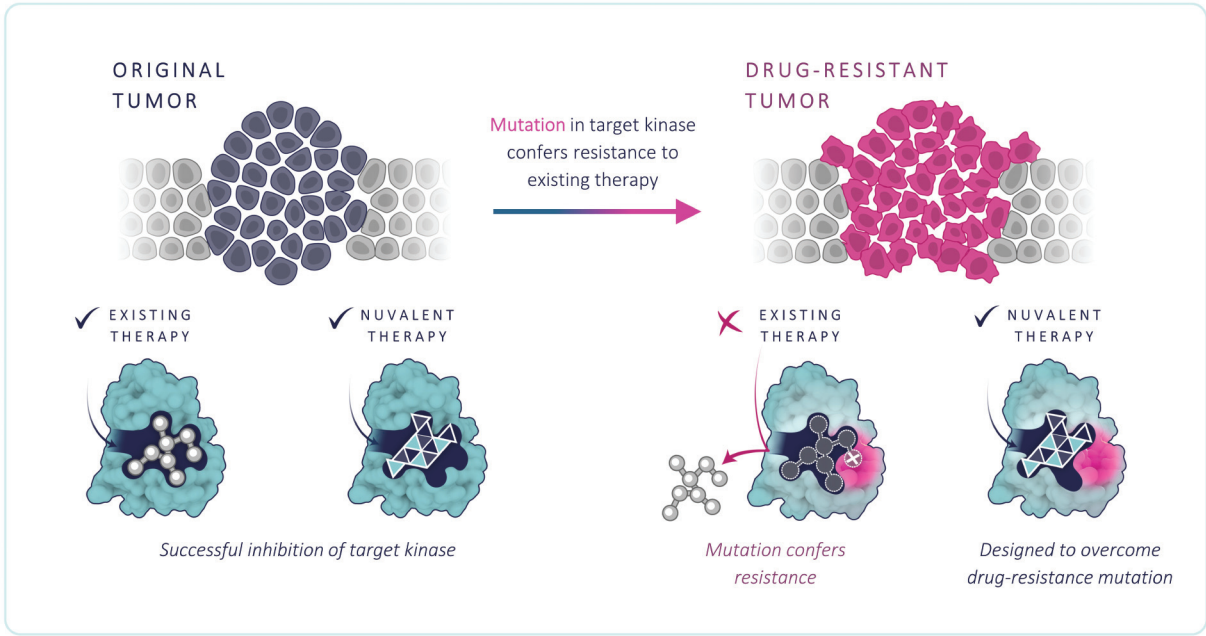
Deep expertise in chemistry and structure-based drug design to achieve precise selectivity ("threading the needle")

We harness our team's deep expertise in chemistry and structure-based drug design to develop product candidates that specifically meet our pre-defined target product profiles with potential to become differentiated therapies that can advance to earlier lines of treatment. This requires the design of innovative structures that are able to 'thread the needle' between achieving high affinity for the kinase target of interest, including drug-resistant variants, while avoiding off-target kinases, in the CNS or in the periphery, associated with dose-limiting toxicities. We believe our purpose-built product candidates have the potential to concurrently address the challenges of kinase resistance, kinase selectivity, and brain penetration.

Addressing kinase resistance

In addition to selectively inhibiting the wild-type kinase, our product candidates are designed to remain active even in the presence of structural changes arising from resistance mutations. This allows our product candidates to potentially treat both the original tumor and tumors with emergent resistance mutations. Figure 2 below illustrates how the unique design of our product candidates may address the challenge of kinase resistance by continuing to bind target kinases, despite structural changes.

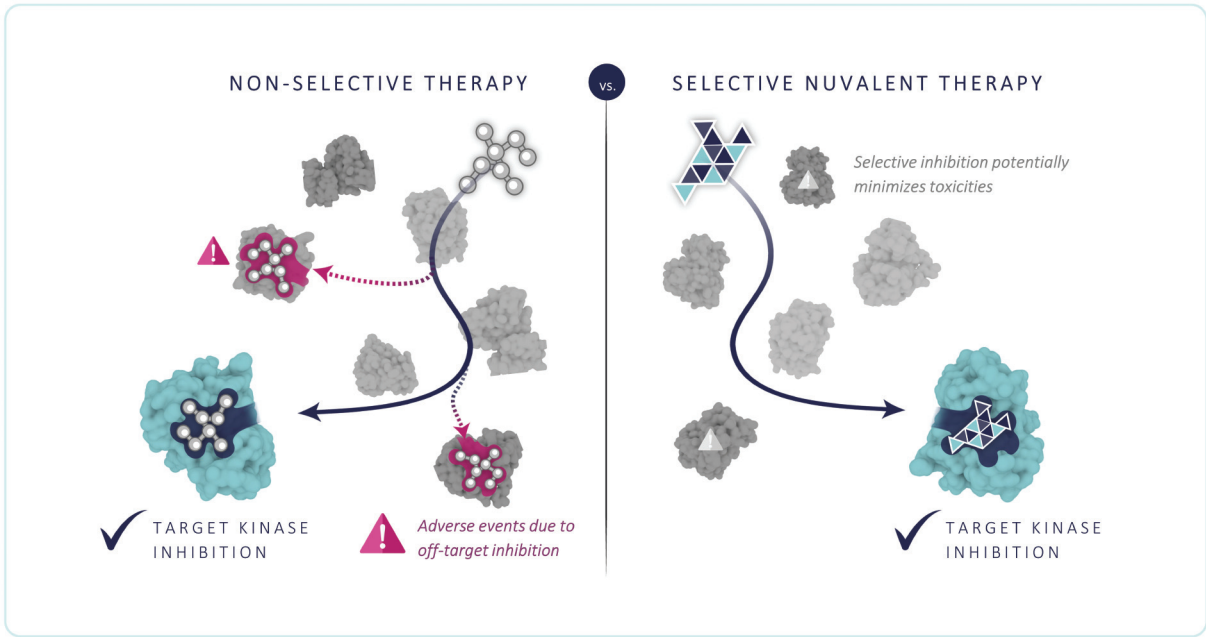
Figure 2. Our ability to address the kinase resistance problem



Addressing kinase selectivity

Many kinases are structurally similar, increasing the potential for off-target binding and related adverse events. We pursue innovative small molecules that can exploit subtle, structural differences across closely related kinases. By prioritizing selectivity, we are able to design inhibitors that have a high affinity for their target kinase relative to other, off-target kinases in order to minimize adverse events and drive durable responses, as illustrated in Figure 3 below.

Figure 3. Our ability to address the kinase selectivity problem



Addressing brain penetration

We pursue product candidates with optimal physical-chemical properties to pass through the BBB, limit recognition by efflux transporters that can actively pump out drug molecules, and reach clinically efficacious concentrations in the brain. Our molecules are designed to achieve these properties while retaining the ability to address kinase resistance to ensure target inhibition, and exquisite kinase selectivity to avoid off-target CNS adverse events.

In summary, we believe a core aspect of our differentiation is the ability to navigate competing molecular challenges in the design of innovative small molecules that address multiple limitations of currently existing therapies to overcome resistance, minimize adverse events, optimize CNS activity, and drive more durable responses. We believe that this ability not only allows us to clearly define an addressable market opportunity, but also provides us with the possibility to move into earlier lines of treatment.

Efficient drug discovery and development

We believe our approach may enable us to develop drugs with an increased probability of clinical success while potentially reducing the cost and risk of drug discovery and development.

We prioritize clinically proven kinase targets in well-defined patient populations, to leverage existing tools and processes for the investigation of clinically proven kinase targets to advance drug discovery and development in an efficient manner. Prior clinical experience with approved inhibitors provides increased confidence in observing early objective measures of tumor responses that could inform the pursuit of an expedited development path. Moreover, learnings from earlier generations of kinase inhibitors may be leveraged to accelerate patient identification and enrollment in clinical trials.

We streamline the discovery process through clear, pre-defined selection criteria within our target product profiles. Once we have developed product candidates that meet these criteria, we continue to advance our programs with discipline and focus our resources on opportunities with the greatest potential for immediate impact.

We design our clinical trials with the goal to efficiently advance clinical development of our product candidates. Pending supportive data, we plan to engage regulators about expedited drug development pathways, such as Fast Track designation, Breakthrough Therapy designation, Priority Review, and other collaborative mechanisms. We believe the profile of our product candidates may allow us to develop breakthrough therapies that have the potential to drive more durable responses and to advance earlier in the treatment paradigm.

Our ROS1 program, NVL-520

Overview

NVL-520 is a differentiated oral small molecule ROS1-selective inhibitor that we are evaluating for the potential treatment of ROS1-positive NSCLC and other solid tumors.

We designed NVL-520 with the aim to overcome several limitations observed with currently available ROS1 inhibitors. Our preclinical data demonstrates that NVL-520 can inhibit both wild-type ROS1 fusions and ROS1 fusions that have developed key resistance mutations, including G2032R. In addition, *in vitro* and *in vivo* studies of NVL-520 have demonstrated its ability to penetrate the brain as well as its superior selectivity for ROS1 over off-target kinases, including the TRK family of kinases, which could help minimize toxicity demonstrated by currently available therapies and therapies in development. We believe this preclinical profile suggests the potential for NVL-520 to be a differentiated ROS1-selective inhibitor that may be able to move earlier in the treatment paradigm.

Clinical investigation of NVL-520 is ongoing in the Phase 1 portion of our ARROS-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-520 in advanced ROS1-positive NSCLC and other solid tumors.

Background and limitations of current ROS1 therapies

ROS1 is an oncogene that encodes the receptor tyrosine kinase ROS1, which can be aberrantly activated by gene rearrangement to drive tumor cell proliferation, survival, and metastasis. In NSCLC, ROS1 rearrangements leading to constitutively active ROS1 fusions (*e.g.,* CD74-ROS1 fusion) are detected in up to 3% of patients. At the time of diagnosis, up to 40% of these patients present with accompanying brain metastases. Beyond NSCLC, ROS1 rearrangements have also been reported across a wide range of solid tumors as well as in some lymphomas.

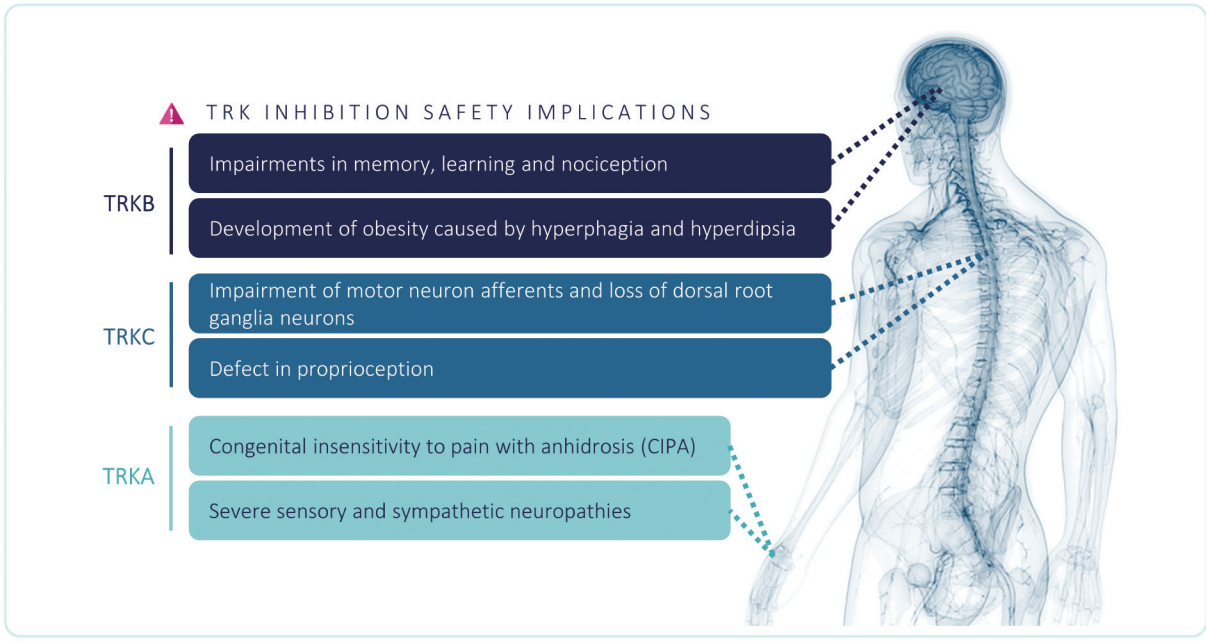
As of February 28, 2022, currently available ROS1 inhibitors include the FDA-approved therapies Xalkori® (crizotinib) and Rozlytrek® (entrectinib). In addition, investigational therapies lorlatinib and repotrectinib are both in active clinical development for ROS1-positive NSCLC. Although these therapies have the potential to improve the lives and outcomes for patients with ROS1-positive NSCLC, many patients still progress. This highlights the significant remaining challenges, including:

1. ***Resistance mutations.*** Secondary kinase domain mutations in ROS1 can confer resistance to and limit the clinical effectiveness of currently available inhibitors. It is estimated that approximately 41% of patients who progress on crizotinib harbor the ROS1 G2032R 'solvent-front' mutation, suggesting a significant population in need of effective therapy. The ROS1 G2032R mutation has also been reported to confer resistance to entrectinib and lorlatinib. Additional, less prevalent crizotinib resistance mutations include the S1986Y/F, D2033N, and 'gatekeeper' L2026M mutations.

2. ***Selectivity.*** Treatment-related CNS adverse events associated with off-target kinase inhibition, specifically TRK, have been observed with entrectinib, repotrectinib, and lorlatinib. Reported TRKB-related adverse events for these brain-penetrant TRK inhibitors include cognitive impairment, mood disorders, sleep disturbances, dizziness, ataxia, and weight gain. Figure 4 below highlights the various CNS-related safety implications associated with inhibition of TRK in the CNS.

3. ***Poor brain penetration.*** Improved options are needed to treat patients with brain metastases, as clinical effectiveness of crizotinib is limited due to its poor brain penetration. Up to 40% of newly diagnosed patients with ROS1-positive NSCLC have brain metastases and there is an increased incidence of brain metastases in patients that progress on ROS1 inhibitors.

Figure 4. Safety implications of TRK inhibition



Target selection & target product profile development: ROS1

Based on the identified limitations, we believe there is a significant medical need for therapeutic agents that could overcome these obstacles, and ultimately provide more durable anti-tumor activity for patients with ROS1-positive cancers.

We have defined, in collaboration with our physician-scientist partners, the following product profile for a ROS1 inhibitor that would address current clinical needs and the limitations of available therapies, and potentially support utility earlier in the treatment paradigm. These criteria include:

- ***Activity against wild-type ROS1 fusions, an oncogenic driver.*** Inhibition of wild-type ROS1 fusions is necessary to treat newly diagnosed patients with ROS1-positive cancers.
- ***Activity against resistance mutations to address the medical need and enable more durable responses.*** Currently, none of the available ROS1 inhibitors adequately address the full spectrum of reported resistance mutations. An inhibitor that can retain activity in the presence of known treatment-emergent resistance mutations presents a potential treatment option for previously treated ROS1-positive NSCLC patients. Moreover, by delivering more effective coverage of known ROS1 resistant variants, this novel compound could limit the appearance of these resistance mutations and lead to more durable responses in earlier lines of therapy.
- ***Avoid inhibition of TRK (TRK sparing) to reduce CNS toxicity.*** TRK inhibition could be the driver behind many of the CNS adverse events observed with brain-penetrant dual TRK/ROS1 inhibitors. Avoiding TRK inhibition may thereby reduce CNS adverse events, minimize dose-limiting toxicities, and enable better target coverage of wild-type ROS1 fusions and ROS1 resistant variants.
- ***Avoid inhibition of other off-target kinases to reduce toxicity.*** Selective inhibition of only ROS1 may further minimize dose-limiting toxicities and enable better target coverage of wild-type ROS1 fusions and ROS1 resistant variants.
- ***Optimized brain penetration to effectively treat patients with brain metastases.*** Approximately 30% of ROS1-positive NSCLC patients have brain metastases at diagnosis. Inadequate brain penetration has significant limitations for crizotinib, which is not efficacious for brain metastases; up to 55% of patients who have disease progression following crizotinib have brain metastases. Although entrectinib has better brain penetration than crizotinib, it has unfavorable CNS toxicities. A brain-penetrant ROS1-selective inhibitor that can avoid CNS adverse events is a needed treatment option for patients with ROS1-positive tumors presenting with or at risk of brain metastases.

Our solution: NVL-520, a ROS1-selective inhibitor

We have designed NVL-520 with the aim to specifically address the target product profile for a novel ROS1-selective inhibitor that can overcome the limitations of current therapies.

In our preclinical studies, we have observed NVL-520 to be a potent, highly selective, and brain-penetrant ROS1 inhibitor that meets our target profile goals and, thus, we believe it is a promising candidate for clinical development. Potency as used in this Annual Report refers to the amount of drug required to produce a pharmacological effect of given intensity and is not a measure of therapeutic efficacy. All statements of the potency, selectivity, and brain penetrance of NVL-520 in this Annual Report have been made based on preclinical *in vitro* or *in vivo* studies that are described in "—Preclinical results" below.

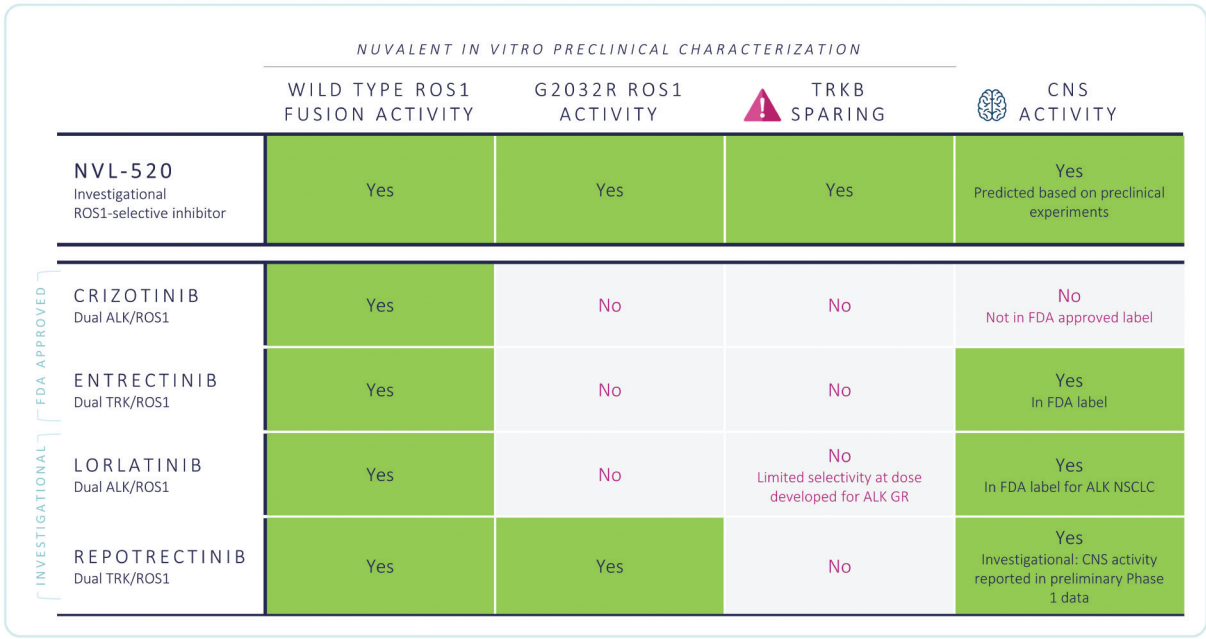
In our preclinical studies, we observed that NVL-520:

- inhibits wild-type ROS1 fusions;
- remains active in tumors that have developed ROS1 resistance mutations, including G2032R;
- is selective for ROS1 over the structurally related TRK family, indicating the potential to minimize TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1 resistance mutations;

- is selective for ROS1 over other off-target kinases; and
- is brain-penetrant in pharmacokinetic and pharmacology studies.

To better understand the potential to differentiate NVL-520 from currently approved and investigational ROS1 inhibitors, we also assessed the ROS1 inhibitors crizotinib, entrectinib, lorlatinib, and repotrectinib in our preclinical studies where possible, under the same study conditions. Although no head-to-head clinical studies have been conducted for these therapies and drug candidates, based on our preclinical evaluation, we observed the drug profiles summarized in Figure 5 below. We believe that this preclinical profile suggests the potential to differentiate NVL-520 from approved or investigational ROS1 inhibitors by addressing the medical needs as defined in our product profile.

Figure 5. NVL-520 is designed with the aim to address medical needs for ROS1-positive NSCLC patients



**No head-to-head clinical studies have been conducted for these therapies and drug candidates versus NVL-520. Clinical investigation of NVL-520 is ongoing. Illustrative representation of the potential ability for currently approved and investigational ROS1 inhibitors to address medical needs for ROS1-positive NSCLC patients. Medical needs have been identified in discussion with our physician-scientist partners. Characterization of wild-type ROS1 fusion activity, G2032R ROS1 activity, and TRKB sparing activity is based on preclinical experiments conducted by Nuvalent. These preclinical experiments were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. TRKB sparing activity refers to whether the drug or drug candidate selectively inhibits its primary development target(s) compared to TRKB. For this analysis, the primary development target for crizotinib, entrectinib, and repotrectinib is considered to be ROS1 wild-type, and the primary development target for lorlatinib, a dual ALK/ROS1 inhibitor, is considered to be ALK G1202R (ALK GR). The primary development targets for NVL-520 include both ROS1 wild-type and the ROS1 G2032R resistance mutation. Characterization of CNS activity for each ROS1 inhibitor is based on FDA labels and/or available clinical and preclinical data independently generated by each sponsor and not based on any preclinical experiments conducted by Nuvalent.*

Based on the preclinical data described below, we believe that NVL-520 has the potential to remain active even in the presence of common resistance mutations, deliver a favorable tolerability profile, and ultimately drive durable responses in both the CNS and in the periphery as a differentiated ROS1-selective inhibitor. The

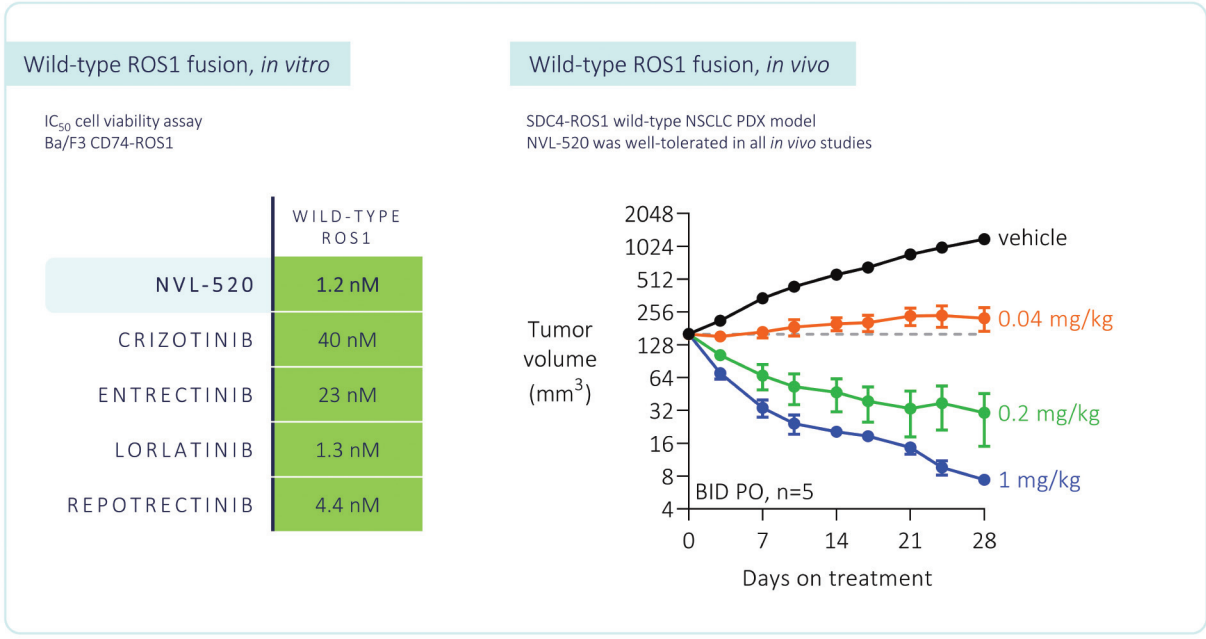
preclinical data described below are included in the active IND for NVL-520, and we believe support the investigation of NVL-520 in patients with previously treated ROS1-positive advanced solid tumors as well as patients with ROS1-positive advanced solid tumors who have not previously received a kinase inhibitor.

Preclinical results

Activity against wild-type ROS1 fusions

We have conducted *in vitro* and *in vivo* experiments in models of wild-type ROS1 fusion-driven NSCLC, where we observed that NVL-520 is a potent preclinical inhibitor of ROS1 and is active against wild-type ROS1 fusions, as summarized in Figure 6. The currently approved and investigational ROS1 inhibitors crizotinib, entrectinib, lorlatinib, and repotrectinib were also tested in this *in vitro* study under the same experimental conditions. *In vitro* measurements of IC_{50} (the concentration required for 50% inhibition of cell viability) were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. NVL-520 potently inhibited Ba/F3 cells expressing the CD74-ROS1 fusion with an IC_{50} of 1.2 nM. Inhibitory activity of NVL-520 against the wild-type ROS1 fusion was confirmed *in vivo*, where NVL-520 induced dose-dependent regression with statistically significant tumor growth inhibition versus vehicle ($p<0.0001$) in the NSCLC patient-derived xenograft (PDX) preclinical model LU-01-0414, which harbors an SDC4-ROS1 fusion.

Figure 6. Preclinical activity of NVL-520 against wild-type ROS1 fusions *in vitro* and *in vivo*



**(Left, in vitro) Ba/F3 cells were engineered to express the CD74-ROS1 fusion. Cells were treated with various currently approved and investigational ROS1 inhibitors under the same experimental conditions (3-fold dilution series, testing in duplicate). Cell viability for each experimental group is reported as half-maximal inhibitory concentration (IC_{50}) measured after 72-hour incubation using CellTiter-Glo reagent and represents the geometric mean of two or more independent experiments with geometric standard deviation of ≤ 1.90. In vitro measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. An IC_{50} of 0-49 nM is indicated as green, an IC_{50} of 50 - 499 nM would be indicated as yellow, and ≥500 nM would be indicated as red.*
(Right, in vivo) SDC4-ROS1 patient-derived xenograft (PDX) tumors were implanted in Balb/c nude mice. Mice were treated with NVL-520 (0.04 mg/kg BID, 0.2 mg/kg BID, or 1 mg/kg BID), or vehicle as a control. Vehicle was 20% HP-β -CD and was used to formulate NVL-520. Average tumor volume (mm3) ± SEM is plotted (n=5 per group). Number of mice was selected assuming signal/noise ratio of ≥ 2.0, 5% significance level, and 80% power versus vehicle. NVL-520 treatment induced significant tumor growth inhibition

compared to vehicle with values ranging from 94% to 115% and adjusted p-values <0.0001 for all doses shown (2-way repeat measure ANOVA with Geisser-Greenhouse correction followed by Dunnett's multiple comparison test).
BID = dosing two times per day, PO = oral administration.
No head-to-head clinical studies have been conducted for these therapies and drug candidates versus NVL-520. Clinical investigation of NVL-520 is ongoing.

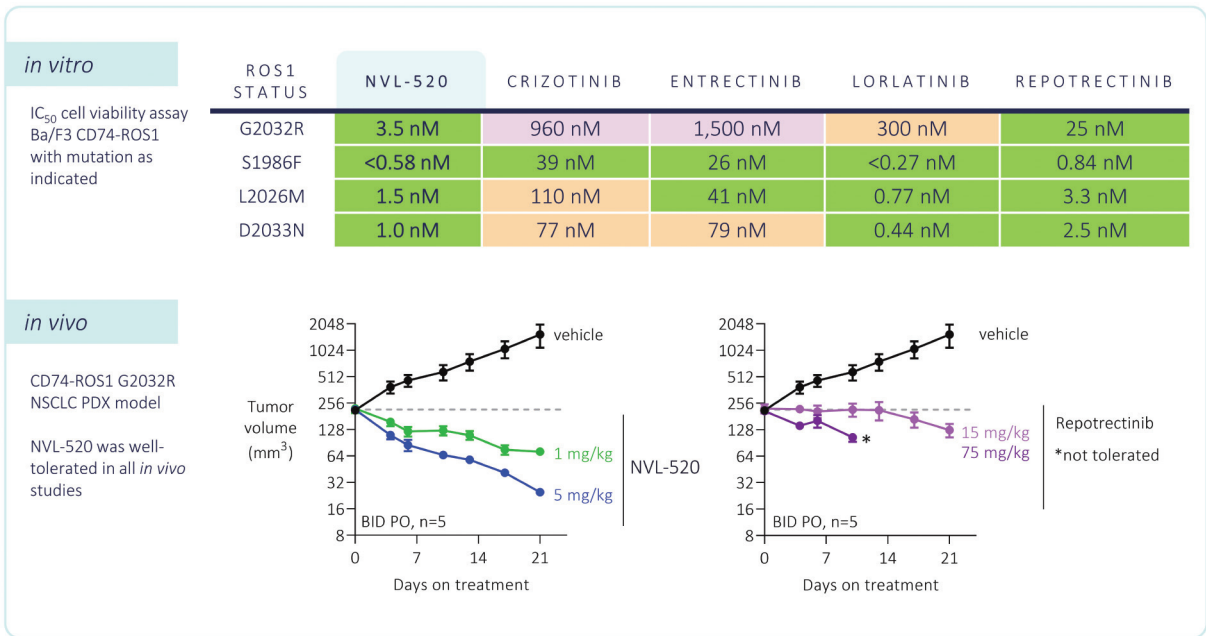
Activity against resistance mutations (G2032R, S1986Y/F, L2026M, D2033N)

We have conducted *in vitro* and *in vivo* experiments in preclinical models of ROS1 fusion-driven NSCLC harboring resistance mutations, where we have observed that NVL-520 potently inhibits ROS1 in the presence of resistance mutations.

In vitro, we observed NVL-520 to potently inhibit Ba/F3 cells expressing CD74-ROS1 fusions that carry clinically relevant drug-resistant mutations, including ROS1 G2032R which confers strong resistance to crizotinib, entrectinib, and lorlatinib. The observed IC_{50} for NVL-520 was at or below single digit nanomolar concentration in all tested cell lines, ranging from <0.58 nM to 3.5 nM. The currently approved and investigational ROS1 inhibitors crizotinib, entrectinib, lorlatinib, and repotrectinib were also tested in this preclinical study under the same experimental conditions. *In vitro* measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

In vivo anti-tumor activity of NVL-520 in comparison to repotrectinib was observed in a murine tumor model derived from a NSCLC patient that progressed on crizotinib with the CD74-ROS1 G2032R mutation. As shown in Figure 7, treatment with NVL-520 induced robust tumor regression at 5 mg/kg BID PO with statistically significant tumor growth inhibition versus vehicle (p<0.0001). Treatment with repotrectinib in the same study resulted in modest regression at a dose of 15 mg/kg and was not tolerated at the higher dose of 75 mg/kg. This study was not designed to determine the statistical significance of differences in tumor regression following treatment with NVL-520 versus repotrectinib.

Figure 7. Preclinical activity of NVL-520 in ROS1 fusion models of NSCLC with clinically relevant resistance mutations *in vitro* and *in vivo*



**(Top, in vitro) Ba/F3 cells were engineered to express the CD74-ROS1 fusion with various resistance mutations as indicated (G2032R, S1986F, L2026M, D2033N). Cells were treated with currently approved and investigational ROS1 inhibitors under the same experimental conditions (3-fold dilution series, testing*

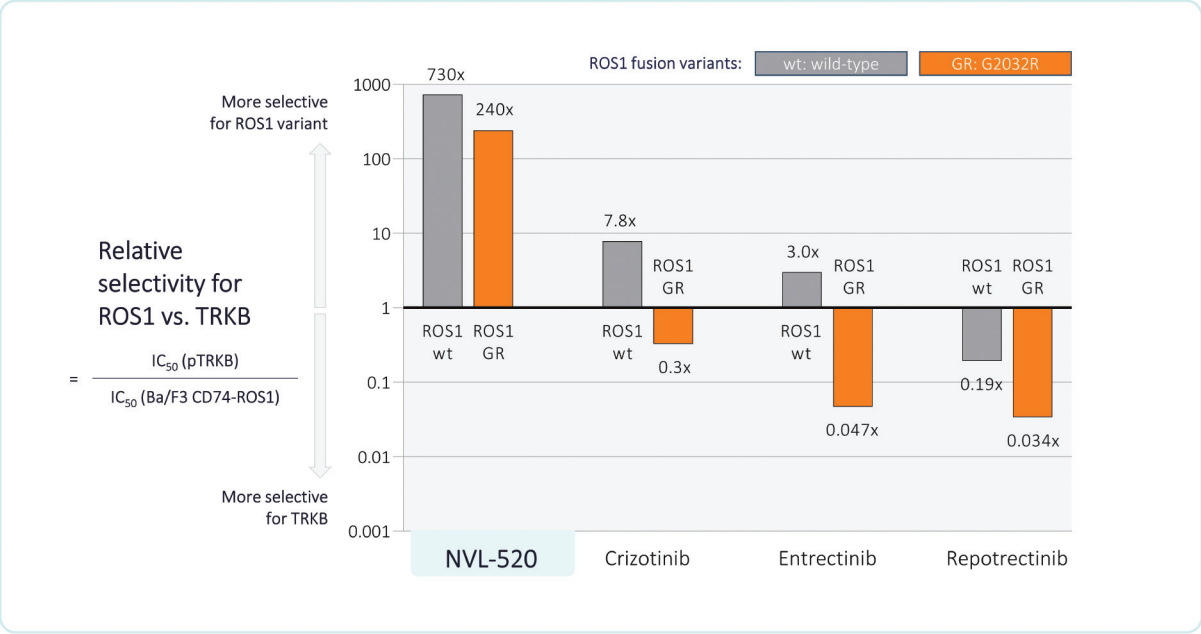
in duplicate). Cell viability for each experimental group is reported as half-maximal inhibitory concentration (IC_{50}) measured after 72-hour incubation using CellTiter-Glo reagent and represents the geometric mean of two or more independent experiments with geometric standard deviation values of ≤ 2.12. An IC_{50} of 0-49 nM is indicated as green, 50 - 499 nM as yellow, and ≥ 500 nM as red.
(Bottom, in vivo) CD74-ROS1 G2032R patient-derived xenograft (PDX) tumors were implanted in Nude-Foxn1nu mice. Mice were treated with NVL-520 (1mg/kg BID or 5 mg/kg BID shown), repotrectinib (15 mg/kg BID or 75 mg/kg BID), or vehicle (20% HP-ß -CD, used to formulate NVL-520). Repotrectinib was dosed as a suspension in 0.5% CMC/1% Tween-80. Average tumor volume (mm3) ± SEM is plotted (n = 5 per group). The number of mice per group was selected assuming signal/noise ratio of ≤ 2.0, 5% significance level, and 80% power versus vehicle. NVL-520 treatment induced regression with significant tumor growth inhibition compared to vehicle with values >110% and adjusted p-value <0.0001 for both doses shown (One-way ANOVA followed by Dunnett's multiple comparisons test).
** = Dosing group suspended due to lack of tolerability.*
BID = dosing two times per day 12 hours apart, PO = oral administration.
No head-to-head clinical studies have been conducted for these therapies and drug candidates versus NVL-520. Clinical investigation of NVL-520 is ongoing.

Avoiding inhibition of TRK

In a preclinical *in vitro* comparison of inhibitory potencies for TRKB and ROS1, we observed that NVL-520 selectively inhibits wild-type ROS1 fusions and ROS1 G2032R mutations whereas dual TRK/ROS1 inhibitors are potent inhibitors for TRK, especially in comparison to inhibition of ROS1 G2032R.

This comparison is presented in Figure 8 below, with taller bars equating to more selective inhibition of CD74-ROS1 (gray bars) or CD74-ROS1 G2032R (orange bars) and fold-selectivity noted above or below each bar. The y-axis depicts the selectivity ratio, with values above 1 indicating more potent activity for the ROS1 variants versus TRKB, and values below 1 indicating more potent activity for TRKB versus the ROS1 variants. As illustrated, NVL-520 achieved favorable selectivity values of 730-fold and 240-fold over TRKB for wild-type ROS1 and ROS1 G2032R, respectively. The TRKB sparing characteristics versus ROS1 variants for the dual ALK/ROS1 inhibitor crizotinib and the dual TRK/ROS1 inhibitors entrectinib and repotrectinib were also measured in this preclinical study under the same conditions. The TRKB sparing characteristics for the dual ALK/ROS1 inhibitor lorlatinib were measured versus ALK and ALK GR, which are considered to be the primary development targets of lorlatinib for this analysis, and are presented in Figure 17 below. *In vitro* measurements of IC_{50} used in the calculation of the selectivity ratios were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

Figure 8. Ability of NVL-520 to avoid off-target TRK inhibition in preclinical assays



**The relative selectivity of ROS1 inhibitors NVL-520, crizotinib, entrectinib, and repotrectinib for ROS1 vs TRKB (gray) and ROS1 G2032R vs TRKB (orange) is shown. The y-axis depicts the selectivity ratio, with values above one indicating more potent activity for the ROS1 variants versus TRKB, and values below one indicating more potent activity for TRKB versus the ROS1 variants. Relative selectivity is calculated by quantifying the cellular BNDF-stimulated TRKB phosphorylation half-maximal inhibitory concentration (IC_{50}) using Ba/F3 cells expressing TRKB and comparing it to the IC_{50} measured in a 72-hour viability assay with Ba/F3 CD74-ROS1 (ROS1 wild-type) cells or Ba/F3 CD74-ROS1 G2032R (ROS1 GR) cells. IC_{50} values represent the geometric mean of two or more independent experiments. In vitro measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.*

No head-to-head clinical studies have been conducted for these therapies and drug candidates versus NVL-520. Clinical investigation of NVL-520 is ongoing.

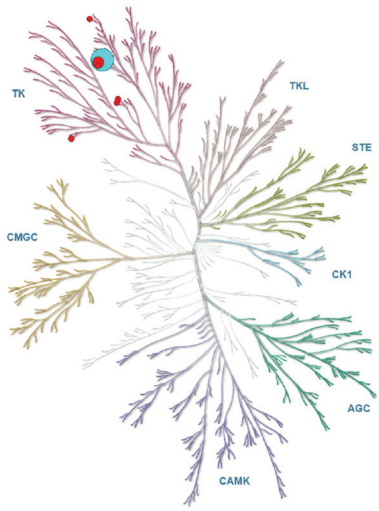
Avoiding inhibition of other off-target kinases

A preclinical kinase selectivity screen showed that NVL-520 is highly selective for ROS1. Across a panel of 335 wild-type kinases, only ALK is inhibited with an $IC_{50} \leq 10$-fold of ROS1, and only five other kinases are inhibited with $IC_{50} \leq 50$-fold of ROS1, as depicted by the red circles in Figure 9 below. The vast majority of kinases (328 kinases) are inhibited with $IC_{50} > 50$-fold of ROS1 and are not plotted.

Figure 9. Selectivity of NVL-520 for ROS1 over other kinases in a preclinical assay

SELECTIVITY INDEX Relative to ROS1-wt	KINASE
1x	ROS1
1 – 10x	ALK
10 – 50x	LTK, FAK, PYK2, TRKB, FER
>50x	328 other kinases

$$\text{Selectivity index} = \frac{IC_{50}\text{ (kinase of interest)}}{IC_{50}\text{ (ROS1 wild-type)}}$$

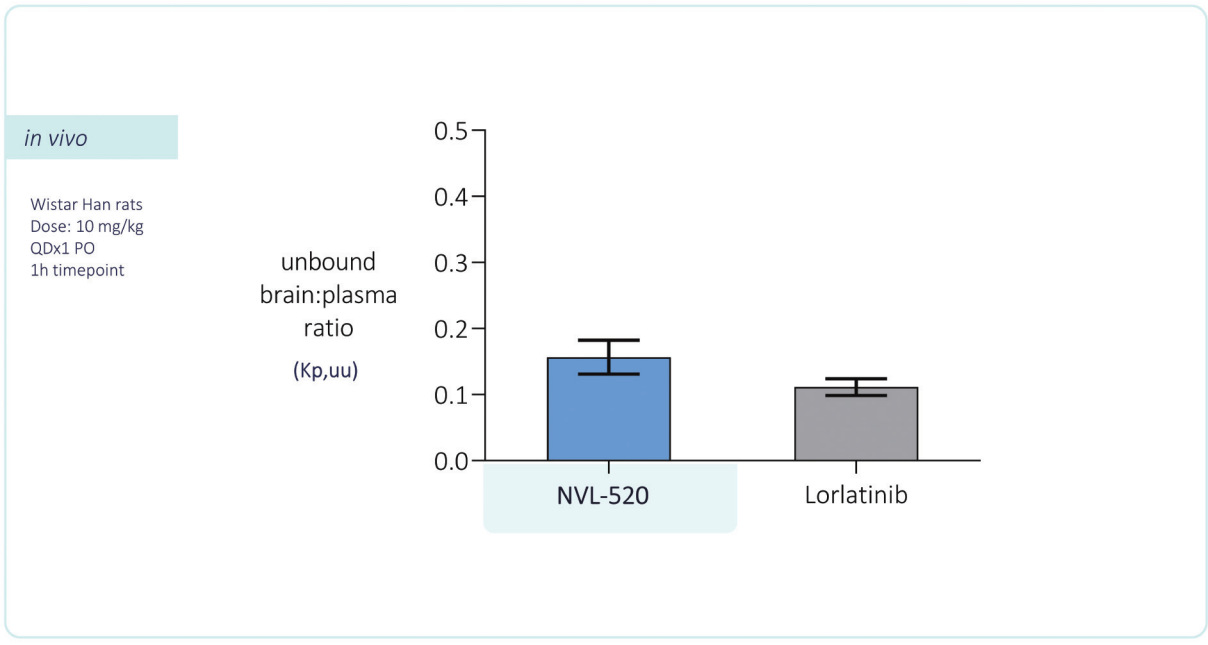


**Results of kinase selectivity screen for NVL-520 (Wild-Type Kinase Panel, Reaction Biology, Germany), displayed on a kinome tree. The panel includes 335 wild-type kinases. The selectivity index of NVL-520 for ROS1 wild-type versus all other tested kinases was calculated as IC_{50} of NVL-520 for the kinase of interest / IC_{50} of NVL-520 for ROS1 wild-type. For each kinase of interest, a selectivity index greater than 1 indicates that NVL-520 is selective for ROS1 over the other kinase. The size of the red circles corresponds to the selectivity index, or IC_{50} relative to ROS1. Kinases with IC_{50} > 50-fold of ROS1 IC_{50} are not plotted. Due to limitations of this biochemical assay, the actual fold selectivity over TRKB may be greater than shown. The selectivity of NVL-520 for ROS1 wild-type and ROS1 resistance variants over TRKB was further characterized in a more physiologically relevant assay as presented in Figure 8 above.*

Optimized brain penetration

We conducted a pharmacokinetic experiment where the preclinical brain exposure of NVL-520 and lorlatinib, a highly brain-penetrant kinase inhibitor, were measured in parallel in rodents. NVL-520 and lorlatinib exhibited similar unbound brain-to-plasma ratios as shown in Figure 10 below, suggesting that NVL-520 may have similarly high brain penetrance in patients. This experiment was not powered to determine the statistical significance of differences in Kp,uu for NVL-520 versus lorlatinib.

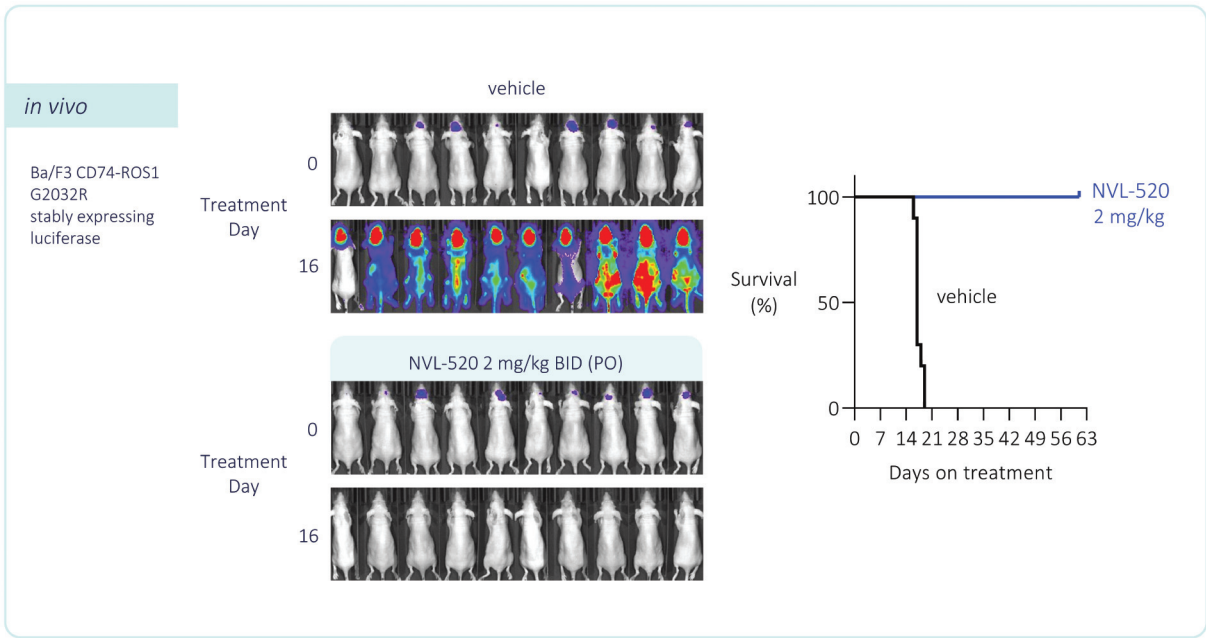
Figure 10. Preclinical brain penetrance of NVL-520 and CNS-active drug loralatinib



**Wistar Han rats were administered a single oral dose (QDx1 PO) of 10 mg/kg NVL-520 or lorlatinib. After one hour, plasma and brain tissue were collected and analyzed to determine Kp,uu, a measure of brain penetration calculated as the ratio of unbound drug in the brain to unbound drug in the plasma outside of the brain. Average Kp,uu ± SEM is plotted (n=3). This experiment was not powered to determine the statistical significance of differences in Kp,uu for NVL-520 versus lorlatinib. No head-to-head clinical studies have been conducted for lorlatinib versus NVL-520. Clinical investigation of NVL-520 is ongoing.*

In an *in vivo* mouse intracranial tumor model of Ba/F3 CD74-ROS1 G2032R luciferase, treatment with NVL-520 reduced brain tumors and demonstrated a significant extended median survival of more than three-fold compared to the vehicle ($p<0.0001$), as seen in Figure 11.

Figure 11. CNS anti-tumor activity of NVL-520 in an *in vivo* preclinical model



**(Left) Ba/F3 cells were engineered to express the CD74-ROS1 fusion with the G2032R resistance mutation, and luciferase to enable bioluminescence imaging. These cells were stereotactically implanted into the right forebrains of Balb/c nude mice. After five days, mice were randomized based on mean bioluminescence signal and treated orally BID with NVL-520 (2 mg/kg shown) or vehicle (20% HP-β -CD). Images of tumor burden on day 16 following treatment initiation are shown, where color represents luminescence as an indicator of tumor burden on a color scale from blue = 10^6 (lower tumor burden) to red = 10^8 photons/sec/cm2/sr (higher tumor burden).*
(Right) A survival analysis from this same experiment is presented, with vehicle n=10 and NVL-520 n=7 (n=3 from the initial n=10 assigned to the NVL-520 dosing group were randomly removed from survival analysis for pharmacokinetic measurements). Number of mice per group was selected assuming signal/noise ratio of ≥ 1.4, 5% significance level, and 80% power versus vehicle. Median survival was 16.5 days for vehicle group and >61 days for the NVL-520-treated group, corresponding to a significant median overall survival extension >3.7-fold (P-value < 0.0001, log-rank Mantel-Cox test).
BID = dosing two times per day, PO = oral administration.

Clinical development plan: NVL-520

Clinical investigation of NVL-520 is ongoing in the Phase 1 portion of our ARROS-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-520 in advanced ROS1-positive NSCLC and other solid tumors.

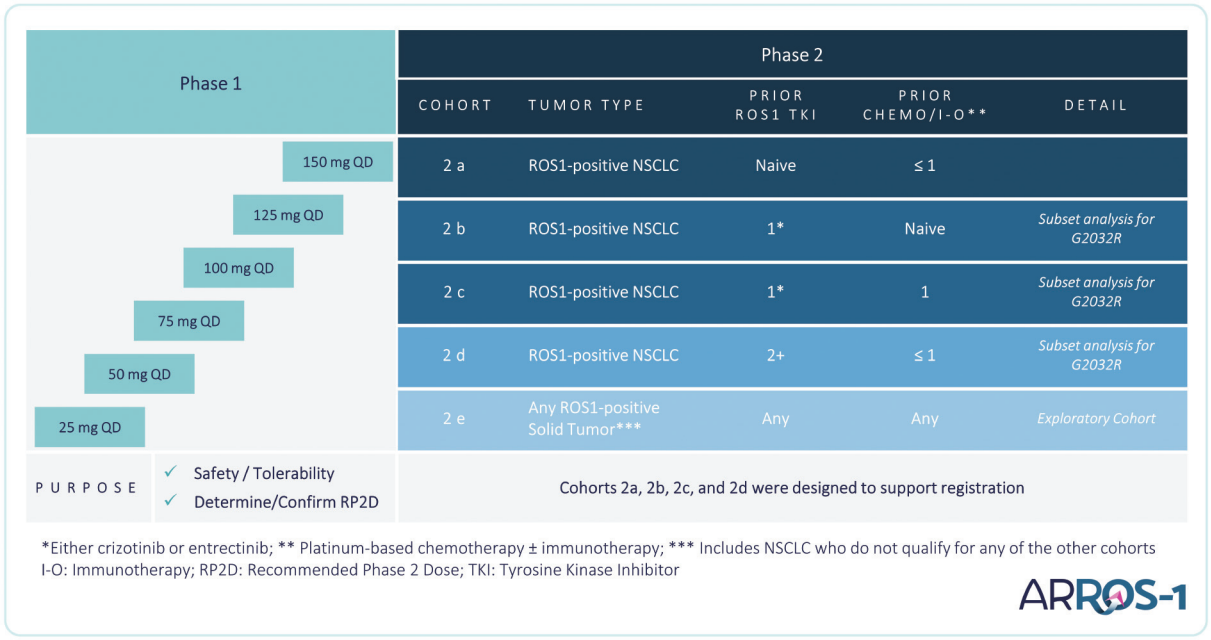
The ongoing ARROS-1 study is designed as a Phase 1/2 trial under a combined clinical trial protocol, where a Phase 1 dose escalation portion has the potential to transition directly into a Phase 2 multiple cohort expansion portion once a safe and tolerable dose is determined as the recommended RP2D. We also plan to conduct an End of Phase 1 meeting with the FDA. This planned study design is depicted in Figure 12 below.

The Phase 1 portion of the clinical trial is designed to evaluate the overall safety and tolerability of NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors, as well as to determine the RP2D, characterize the pharmacokinetic profile, and evaluate preliminary anti-tumor activity of NVL-520.

The planned Phase 2 portion of the clinical trial is designed to evaluate the overall activity of NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors, examining several specific cohorts of patients based on prior anti-cancer therapies they have received. Phase 2 cohorts have been designed to support potential registration in either kinase inhibitor naïve or previously treated ROS1-positive NSCLC patients.

Based on the totality of clinical data from the Phase 1 portion of the trial, and if supported by an acceptable safety profile, favorable pharmacokinetics and pharmacodynamics, and a positive efficacy signal in patients with ROS1-positive solid tumors, we will continue to engage with the FDA and other regulatory agencies to discuss our plan for the Phase 2 portion of the trial, and specifically, its potential to support registration in key populations with significant medical need.

Figure 12. ARROS-1: Ongoing first-in-human clinical trial of NVL-520 in advanced ROS1-positive NSCLC and other solid tumors



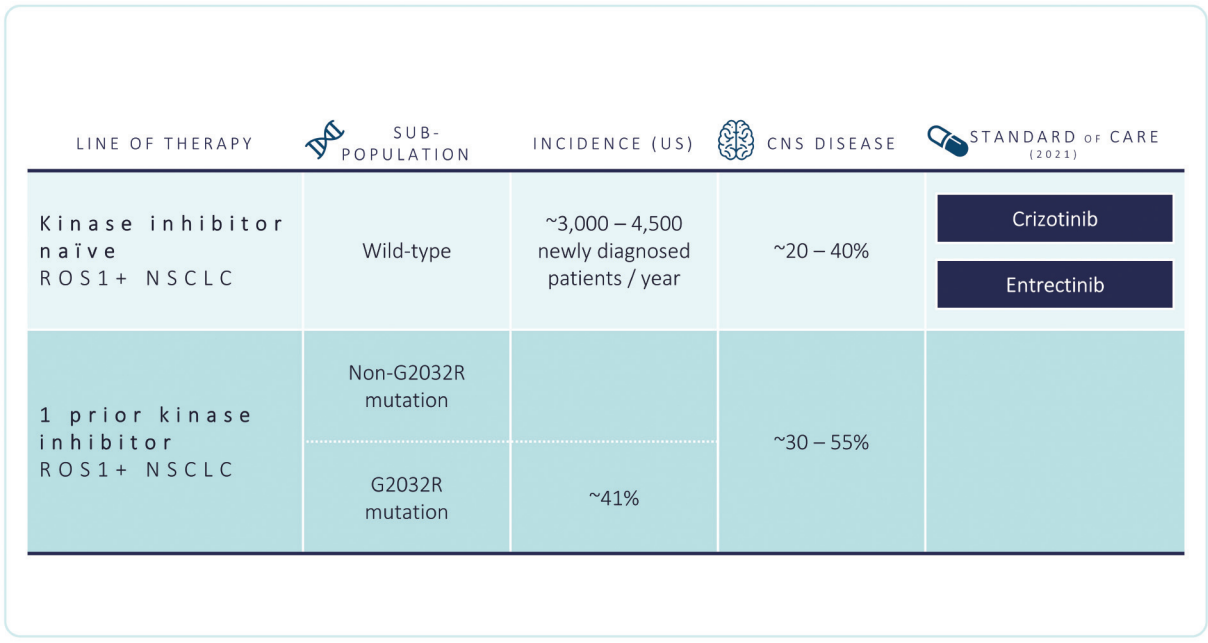
We plan to initially enroll patients in the Phase 1 part of the study in the U.S. and in Europe, utilizing some of the leading cancer centers with experience in early clinical studies with precision oncology medicines, while maintaining active engagement with leading clinical and translational thought leaders. Pending favorable data from the Phase 1 portion of the study, we expect to expand the Phase 2 portion into additional geographies in order to support the potential global registration of NVL-520.

The design of the Phase 1/2 study, including the potential for the Phase 2a, 2b, 2c and 2d cohorts to be supportive of potential registration, has been discussed with the FDA. Pending supportive data, we plan to engage with regulators about expedited drug development pathways, such as Fast Track designation, Breakthrough Therapy designation, Priority Review designation, and other collaborative mechanisms. We also intend to leverage our Phase 2e exploratory cohort to investigate the safety and activity of NVL-520 in other tumor types with ROS1 fusions.

ROS1 market opportunity

There are approximately 3,000 to 4,500 newly diagnosed patients a year in the U.S. with ROS1-positive NSCLC, representing up to 3% of all NSCLC patients. At the time of diagnosis, up to 40% of ROS1-positive NSCLC patients present with accompanying brain metastases, requiring therapy with the ability to penetrate the BBB. Based on a study of 16 patients progressing on crizotinib, it is estimated that approximately 41% of patients who progress on crizotinib harbor the ROS1 G2032R mutation, suggesting a significant population in need of effective therapy. The ROS1-positive NSCLC market overview is summarized in Figure 13 below.

Figure 13. ROS1-positive NSCLC market overview



We have designed our Phase 2 cohorts to potentially support registration in either TKI naïve or previously treated ROS1-positive NSCLC patients. Beyond NSCLC, we believe that NVL-520 has the potential to treat pediatric and adult patients with other tumor types that contain ROS1 fusions, such as gliomas, inflammatory myofibroblastic tumors, anaplastic large-cell lymphoma, and skin, liver, thyroid, ovarian, gastric, and pancreatic cancers. As part of the Phase 2 portion of our Phase 1/2 clinical trial, we intend to enroll a single exploratory cohort of patients with ROS1-positive cancers outside of NSCLC.

Our ALK program, NVL-655

Overview

NVL-655 is a differentiated oral small molecule ALK-selective inhibitor, which we are evaluating for the potential treatment of ALK-positive NSCLC and other advanced cancers.

We designed NVL-655 with the aim to overcome several limitations observed with currently available ALK inhibitors. Our preclinical data demonstrates that NVL-655 can inhibit both wild-type ALK fusions and ALK fusions that have developed resistance mutations to first-, second-, and third-generation ALK inhibitors, including tumors with solvent-front or other compound mutations. In addition, *in vitro* and *in vivo* studies of NVL-655 have demonstrated its ability to penetrate the brain as well as its superior selectivity for ALK over off-target kinases, including the TRK family of kinases, which could help minimize toxicity demonstrated by previous generation inhibitors. We believe this preclinical profile suggests the potential for NVL-655 to be a differentiated, ALK-selective inhibitor that may be able to address medical needs for patients previously treated with currently approved kinase inhibitors that target ALK, and that may be able to move earlier in the treatment paradigm.

We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the Phase 1 portion of our planned ALKOVE-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022.

Background and limitations of current ALK therapies

ALK is an oncogene that encodes the receptor tyrosine kinase ALK, which can be aberrantly activated by gene rearrangement or point mutation to drive tumor cell proliferation, survival, and metastasis. In NSCLC, ALK rearrangements leading to ALK fusions (*e.g.*, EML4-ALK fusion) are detected in approximately 5% of patients. At the time of initial diagnosis, up to 40% of these patients present with accompanying brain metastases. Beyond NSCLC, ALK fusions have also been reported in various other solid tumors as well as some lymphomas.

As of February 28, 2022, five kinase inhibitors have been approved by the FDA for front-line treatment of ALK-positive NSCLC. They are categorized into three generations: first generation (Xalkori® (crizotinib)); second generation (Alcensa® (alectinib), Alunbrig® (brigatinib), and Zykadia™ (ceritinib)); and third generation (Lorbrena® (lorlatinib)). First-line alectinib is the preferred choice of physicians. While lorlatinib has demonstrated activity in NSCLC patients that have progressed on previous generations of inhibitors, there are no approved treatments for patients that have progressed on this treatment.

Although the current FDA-approved therapies have the potential to improve the lives and outcomes for patients with ALK-positive cancers, many patients still progress on available therapies. This highlights the significant remaining challenges, including:

1. ***Resistance mutations.*** Durability of response to currently approved inhibitors has been limited in many cases by the emergence of treatment-related mutations in ALK that lead to resistance to therapy. There is growing clinical evidence that suggests that different resistance mutation patterns may emerge depending on the ALK kinase inhibitor used and the line of therapy. These mutations include the 'solvent-front' mutation G1202R, which has been observed in approximately 35% of patients that have progressed on crizotinib, alectinib, brigatinib, or ceritinib, as well as G1202R+ compound mutations, which have been observed upon sequential alectinib/lorlatinib treatment.
2. ***Selectivity.*** Treatment-related CNS adverse events associated with off-target kinase inhibition, specifically attributed to TRKB, have been observed with lorlatinib. Reported TRKB-related adverse events for this brain-penetrant TRK inhibitor include cognitive impairment, mood disorders, sleep disturbances, dizziness, ataxia, and weight gain.

Target selection & target product profile development: ALK

Based on the identified limitations, we believe there is a significant medical need for therapeutic agents that could overcome these obstacles, and ultimately provide more durable anti-tumor activity for patients with ALK-positive cancers.

We have defined, in collaboration with our physician-scientist partners, the following target product profile for an ALK inhibitor that would address current clinical needs and the limitations of available therapies, and potentially support utility earlier in the treatment paradigm. These criteria include:

- ***Activity against wild-type ALK fusions, an oncogenic driver.*** Inhibition of wild-type ALK fusions is necessary to treat newly diagnosed patients with ALK-positive cancers.
- ***Activity against resistance mutations to address the medical need and enable more durable responses.*** Currently, none of the available ALK kinase inhibitors adequately address the full spectrum of reported resistance mutations. An inhibitor that can retain activity in the presence of known treatment-emergent resistance mutations may provide a potential option for previously treated ALK-positive NSCLC patients. Moreover, by more effective coverage of known ALK mutation variants, this novel compound could limit the appearance of these resistance mutations and lead to more durable responses in earlier lines of therapy.
- ***Avoid inhibition of TRK (TRK sparing) to reduce CNS toxicity.*** TRK inhibition could be the driver behind many of the CNS adverse events observed with the brain-penetrant ALK inhibitor, lorlatinib. Avoiding TRK inhibition may thereby reduce CNS adverse events, minimize dose-limiting toxicities, and enable better target coverage of wild-type ALK fusions and ALK resistant variants.

- ***Avoid inhibition of other off-target kinases to reduce toxicity.*** Selective inhibition of only ALK may further minimize dose-limiting toxicities and enable better target coverage of wild-type ALK fusions and ALK resistant variants.
- ***Optimized brain penetration to effectively treat patients with brain metastases.*** Up to 40% of ALK-positive NSCLC patients have brain metastases at diagnosis, and incidence of brain metastases increases to more than 60% in later lines of therapy, highlighting the need for a brain-penetrant ALK-selective inhibitor that can avoid CNS adverse events.

Our solution: NVL-655, an ALK-selective inhibitor

We have designed NVL-655 with the aim to specifically address the target product profile for a novel ALK-selective inhibitor that can overcome the limitations of current therapies.

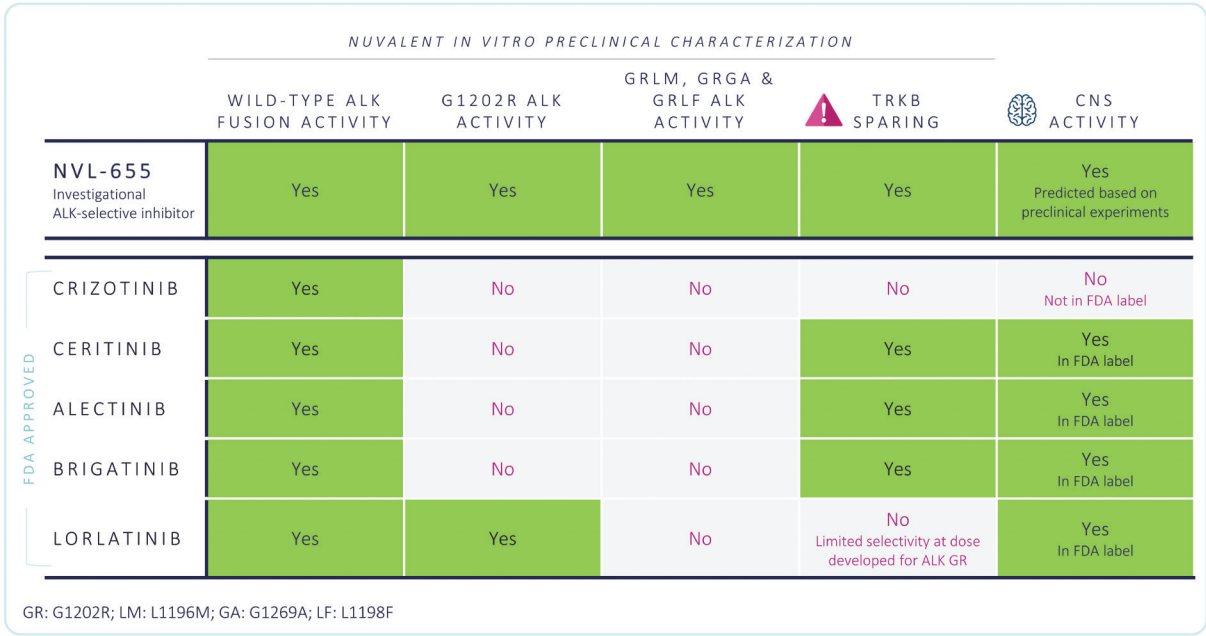
In our preclinical studies, we have observed NVL-655 to be a potent, highly selective, brain-penetrant ALK inhibitor that meets our target profile goals and thus, we believe it is a promising candidate for clinical development. Potency as used in this Annual Report refers to the amount of drug required to produce a pharmacological effect of given intensity and is not a measure of therapeutic efficacy. All statements of the potency, selectivity and brain penetrance of NVL-655 in this Annual Report have been made based on preclinical *in vitro* or *in vivo* studies that are described in "—Preclinical results" below.

In our preclinical studies, we observed that NVL-655:

- inhibits wild-type ALK fusions;
- remains active in tumors that have developed resistance to first-, second-, and third generation ALK inhibitors, including tumors with the solvent-front G1202R single mutation, G1202R+ compound mutations, or a non-G1202R mutation;
- is selective for ALK over the structurally related TRK family, indicating the potential to minimize TRK-related CNS adverse events seen with other ALK inhibitors and drive more durable responses for patients with ALK resistance mutations;
- is selective for ALK over other off-target kinases; and,
- is brain-penetrant in pharmacokinetic studies.

To better understand the potential to differentiate NVL-655 from currently approved ALK inhibitors, we also assessed the ALK inhibitors crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib in our preclinical studies where possible, under the same study conditions. Although no head-to-head clinical studies have been conducted for these therapies versus NVL-655, based on our preclinical evaluation, we observed the drug profiles summarized in Figure 14 below. We believe that this preclinical profile suggests the potential to differentiate NVL-655 from approved ALK inhibitors by addressing the medical needs as defined in our target product profile.

Figure 14. NVL-655 is designed with the aim to address medical needs for previously treated ALK-positive NSCLC patients



** No head-to-head clinical studies have been conducted for these therapies versus NVL-655. No clinical studies have been conducted for NVL-655. Illustrative representation of the potential ability for currently approved ALK inhibitors to address medical needs for ALK-positive NSCLC patients. Medical needs have been identified in discussion with our physician-scientist partners. Characterization of wild-type ALK fusion activity, activity against ALK single resistance mutation G1202R, activity against compound mutations GRLM, GRGA, and GRLF, and TRKB sparing activity is based on preclinical experiments conducted by Nuvalent. These preclinical experiments were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. TRKB sparing activity refers to whether the drug or drug candidate selectively inhibits its primary development target(s) compared to TRKB. For this analysis, the primary development target for crizotinib, ceritinib, alectinib, and brigatinib is considered to be ALK wild-type, and the primary development target for lorlatinib is considered to be ALK G1202R. The primary development targets for NVL-655 include ALK wild-type as well as ALK single and compound resistance mutations G1202R, GRLM, GRGA, and GRLF. Characterization of CNS activity for each ALK inhibitor is based on FDA labels and/or available clinical and preclinical data independently generated by each sponsor and not based on any preclinical experiments conducted by Nuvalent.*

Based on the preclinical data described below, we believe that NVL-655 has the potential to remain active even in the presence of common resistance mutations, deliver a favorable tolerability profile, and ultimately drive durable responses in both the CNS and in the periphery as a differentiated ALK-selective inhibitor. The preclinical data described below are included in the active IND for NVL-655, and we believe that they are supportive of the investigation of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors.

Preclinical results

Activity against wild-type ALK fusions

We have conducted *in vitro* experiments in cellular models of wild-type ALK fusion-driven NSCLC, where we observed that NVL-655 is a potent preclinical inhibitor of ALK, as summarized in Figure 15. NVL-655 inhibited human cancer cell lines and Ba/F3 cells expressing EML4-ALK fusions with IC_{50} (the concentration required for 50% inhibition of cell viability) in the low single digit nanomolar range (0.70 nM to 2.0 nM). The currently FDA approved therapies for patients with ALK-positive NSCLC (crizotinib, ceritinib, alectinib, brigatinib, and

lorlatinib) were also tested in this preclinical study under the same experimental conditions. *In vitro* measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

Figure 15. Preclinical activity of NVL-655 against wild-type ALK fusions *in vitro*

Wild-type ALK fusion, *in vitro*

IC_{50} cell viability assay (nM)	NVL-655	CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
NCI-H2228 (EML4-ALK v3)	0.70 nM	90 nM	55 nM	13 nM	13 nM	< 1.1 nM
NCI-H3122 (EML4-ALK v1)	2.0 nM	180 nM	48 nM	22 nM	22 nM	3.5 nM
Ba/F3 EML4-ALK v1	1.6 nM	270 nM	90 nM	25 nM	42 nM	4.2 nM

**Human ALK-positive cancer cell lines (NCI-H2228, NCI-H31222) and Ba/F3 cells engineered to express the EML4-ALK v1 fusion were treated with various ALK inhibitors under the same experimental conditions (3-fold dilution series, testing in duplicate). Cell viability for each experimental group is reported as half-maximal inhibitory concentration (IC_{50}) measured after 72-hour incubation using CellTiter-Glo reagent and represents the geometric mean of two or more independent experiments with geometric standard deviation values of ≤ 1.9. In vitro measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. An IC_{50} of 0-49 nM is indicated as green, 50 - 499 nM as yellow, and ≥ 500 nM would be indicated in red.*
No head-to-head clinical studies have been conducted for these therapies versus NVL-655. No clinical studies have been conducted for NVL-655.

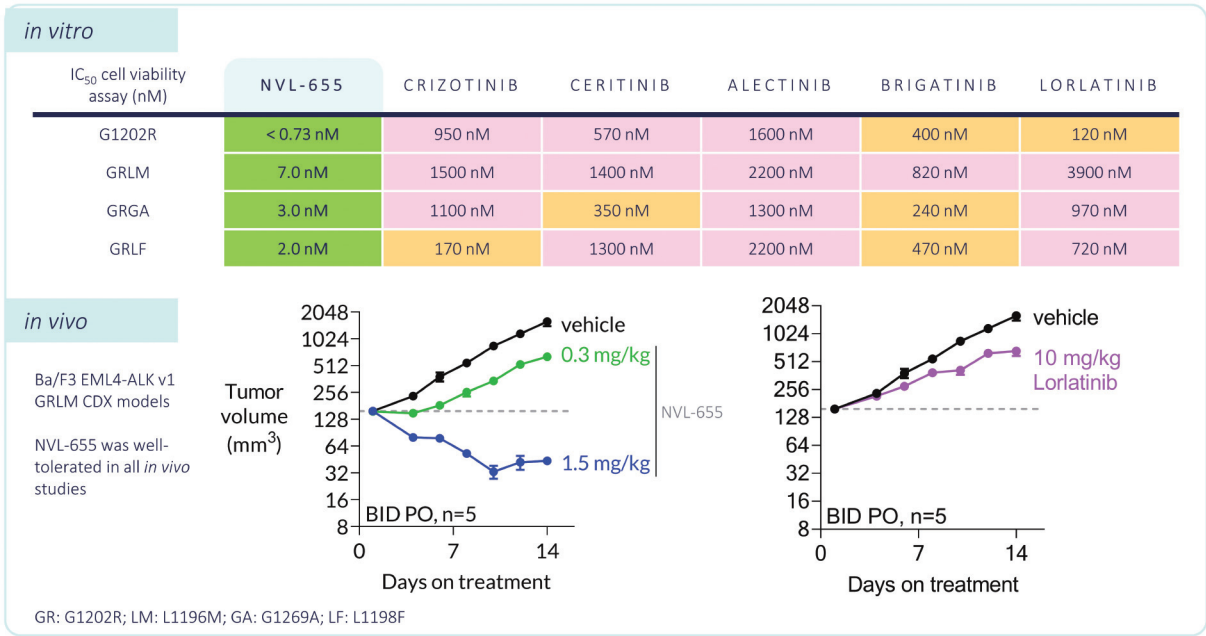
Activity against resistance mutations (G1202R+ and non-G1202R)

We have conducted *in vitro* and *in vivo* experiments in preclinical models of ALK fusion-driven NSCLC harboring various resistance mutations where we have observed that NVL-655 potently inhibits ALK in the presence of resistance mutations that other approved therapies have not been able to address.

In vitro, NVL-655 potently inhibited Ba/F3 cells expressing ALK fusions that carried clinically relevant G1202R+ drug-resistant mutations, as shown in Figure 16 below. The observed IC_{50} for NVL-655 was at single digit nanomolar concentrations across all tested cell lines, ranging from <0.73 nM to 7.0 nM. The currently approved ALK inhibitors crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib were also tested in this preclinical study under the same experimental conditions. Most notably, NVL-655 potently inhibited cells with the GRLM compound mutation, which confers resistance to all of the currently FDA approved ALK inhibitors, with an observed IC_{50} of 7.0 nM versus an IC_{50} of 820 nM to 3900 nM for the approved ALK inhibitors. *In vitro* measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

In vivo anti-tumor activity of NVL-655 was demonstrated in a murine Ba/F3 model of NSCLC harboring the EML4-ALK v1 fusion with a GRLM mutation. Lorlatinib was also tested in this preclinical study under the same experimental conditions as shown in Figure 16, and both of these compounds were well-tolerated upon oral BID dosing. Treatment with NVL-655 showed dose-dependent tumor regression through 14 days, with statistically significant tumor growth inhibition versus vehicle ($p \leq 0.0001$). Lorlatinib modestly inhibited tumor growth at the 10 mg/kg BID PO dose tested; 5 mg/kg BID PO lorlatinib preclinically approximates the plasma exposure of the human dose of 100 mg QD. These findings are consistent with clinical reports of the detection of the GRLM compound mutation in patients that have progressed on lorlatinib. This study was not designed to determine the statistical significance of differences in tumor regression following treatment with NVL-655 versus lorlatinib.

Figure 16. Preclinical activity of NVL-655 against G1202R+ drug-resistant models of ALK-positive NSCLC



**(Top, in vitro) Ba/F3 cells were engineered to express the EML4-ALK v1 fusion with various single and compound resistance mutations as indicated (G1202R, GRLM, GRGA, GRLF). Cells were treated with various ALK inhibitors under the same experimental conditions (3-fold dilution series, testing in duplicate). Cell viability for each experimental group is reported as half-maximal inhibitory concentration (IC_{50}) measured after 72-hour incubation using CellTiter-Glo reagent and represents the geometric mean of two or more independent experiments with geometric standard deviation values of ≤ 2.12. An IC_{50} of 0-49 nM is indicated as green, 50 - 499 nM as yellow, and ≥ 500 nM as red.*

(Bottom, in vivo) A xenograft model was created by implanting Balb/c nude mice with Ba/F3 cells engineered to express the EML4-ALK v1 fusion with a G1202R/L1196M resistance mutation. Mice were treated orally with NVL-655 (0.3 mg/kg BID and 1.5 mg/kg BID shown), lorlatinib (10 mg/kg BID), or vehicle (20% HP-β -CD). Average tumor volume (mm3) ± SEM is plotted (n=5 per group). Number of mice per group was selected assuming signal/noise ratio of ≥ 2.0, 5% significance level, and 80% power versus vehicle. NVL-655 at 1.5 mg/kg BID induced regression with significant tumor growth inhibition compared to vehicle (108%, $p \leq 0.0001$, two-way repeat measures ANOVA followed by Tukeys post hoc comparisons of the means).

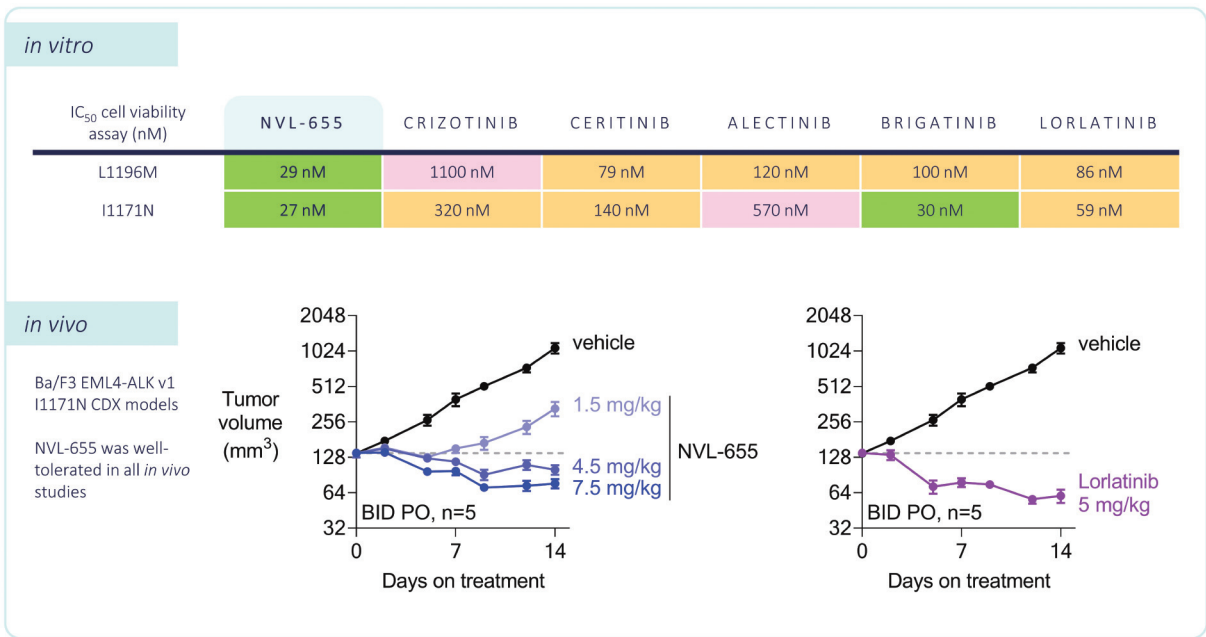
BID = dosing two times per day 12 hours apart, PO = oral administration.

No head-to-head clinical studies have been conducted for these therapies versus NVL-655. No clinical studies have been conducted for NVL-655.

Non-G1202R drug-resistant mutations such as L1196M and I1171N have also been observed in patients following treatment with currently available ALK inhibitors. *In vitro*, NVL-655 inhibited Ba/F3 cells expressing ALK fusions that carried these clinically relevant non-G1202R drug-resistant mutations, as shown in Figure 17 below, at observed IC_{50} values between 25 nM and 30 nM. The currently approved ALK inhibitors crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib were also tested in this preclinical study under the same experimental conditions and their IC_{50} values ranged from 30 nM to 1,100 nM. *In vitro* measurements of IC_{50} were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

In vivo anti-tumor activity of NVL-655 was demonstrated in a murine Ba/F3 model of NSCLC harboring the EML4-ALK v1 fusion with the I1171N mutation. Lorlatinib was also tested in this preclinical study under the same experimental conditions and both of these compounds were well-tolerated upon oral BID dosing. Treatment with NVL-655 showed dose-dependent tumor reduction with statistically significant tumor growth inhibition versus vehicle ($p<0.0001$). Lorlatinib also showed tumor reduction at the 5 mg/kg dose tested, which was selected to preclinically approximate the exposure of the human dose of 100 mg QD. This study was not designed to determine the statistical significance of differences in antitumor activity following treatment with NVL-655 versus lorlatinib.

Figure 17. Preclinical activity of NVL-655 against non-G1202R drug-resistant models of ALK-positive NSCLC



**(Top, in vitro) Ba/F3 cells were engineered to express the EML4-ALK v1 fusion with resistance mutations as indicated (L1196M, I1171N). Cells were treated with various ALK inhibitors under the same experimental conditions (3-fold dilution series, testing in duplicate). Cell viability for each experimental group is reported as half-maximal inhibitory concentration (IC_{50}) measured after 72-hour incubation using CellTiter-Glo reagent and represents the geometric mean of two or more independent experiments with geometric standard deviation values of ≤ 3.0. An IC_{50} of 0-49 nM is indicated as green, 50 - 499 nM as yellow, and ≥ 500 nM as red.*
(Bottom, in vivo) A xenograft model was created by implanting Balb/c nude mice with Ba/F3 cells engineered to express the EML4-ALK v1 fusion with an I1171N resistance mutation. Mice were treated orally with NVL-655 (1.5 mg/kg BID, 4.5 mg/kg BID and 7.5 mg/kg BID), lorlatinib (5 mg/kg BID), or vehicle (20% HP-β -CD). Lorlatinib 5 mg/kg was selected to approximate the exposure of the human dose of 100 mg QD. Average tumor volume (mm3) ± SEM is plotted (n=5 per group). Number of mice per group was selected assuming signal/noise ratio of ≥ 2.0, 5% significance level, and 80% power versus vehicle. NVL-655 at 4.5 mg/kg BID and 7.5 mg/kg BID induced regression with significant tumor growth inhibition compared to vehicle (p≤0.0001, two-way repeat measures ANOVA followed by Tukeys post hoc comparisons of the means).
BID = dosing two times per day 12 hours apart, PO = oral administration.
No head-to-head clinical studies have been conducted for these therapies versus NVL-655. No clinical studies have been conducted for NVL-655.

Avoiding inhibition of TRK

In a preclinical *in vitro* comparison of inhibitory potencies for TRKB and ALK, we observed that NVL-655 selectively inhibits ALK G1202R+ mutations to a greater extent than lorlatinib.

This comparison is presented in Figure 18 below, with taller bars equating to more selective inhibition of wild-type ALK, ALK G1202R, ALK GRLM, or ALK GRGA (gray, orange, green, or blue bars, respectively) and fold-selectivity noted above each bar. The y-axis depicts the selectivity ratio, with values above 1 indicating more potent activity for the ALK variants versus TRKB, and values below 1 indicating more potent activity for TRKB versus the ALK variants. As illustrated, NVL-655 achieved favorable selectivity values of 91-fold to 870-fold over TRKB across all ALK variants shown below. Notably, lorlatinib only provides limited selectivity for ALK G1202R over TRKB in this analysis, consistent with TRKB-related CNS adverse events observed with lorlatinib. The TRKB sparing characteristics versus ALK variants for the ALK inhibitors crizotinib, alectinib, brigatinib, and ceritinib were also measured in this preclinical study under the same conditions. The pTRKB IC_{50} values for alectinib, brigatinib, and ceritinib were > 1 μM, supporting the observation that these compounds are TRKB sparing. *In vitro* measurements of IC_{50} used in the calculation of the selectivity ratios were not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested.

Figure 18. Ability of NVL-655 to avoid off-target TRKB inhibition in preclinical models

**The relative selectivity of ALK inhibitors NVL-655, crizotinib, and lorlatinib for ALK vs TRKB (gray), ALK G1202R versus TRKB (orange), ALK GRLM versus TRKB (green), and ALK GRGA versus TRKB (blue) is shown. The y-axis depicts the selectivity ratio, with values above one indicating more potent activity for the ALK variants versus TRKB, and values below 1 indicating more potent activity for TRKB versus the ALK variants. Relative selectivity is calculated by quantifying the cellular BNDF-stimulated TRKB phosphorylation (pTRKB) half-maximal inhibitory concentration (IC_{50}) using Ba/F3 cells expressing TRKB and comparing it to the IC_{50} measured in a 72-hour viability assay for each inhibitor with Ba/F3 EML4-ALK (ALK wild-type) cells or Ba/F3 EML4-ALK cells with resistance mutations (ALK GR, ALK GRLM, or ALK GRGA). IC_{50} values represent the geometric mean of two or more independent experiments for each inhibitor. pTRKB IC_{50} values for brigatinib, ceritinib, and alectinib were > 1 μM and were not plotted. No head-to-head clinical studies have been conducted for these therapies versus NVL-655. No clinical studies have been conducted for NVL-655.*

Avoiding inhibition of other off-target kinases

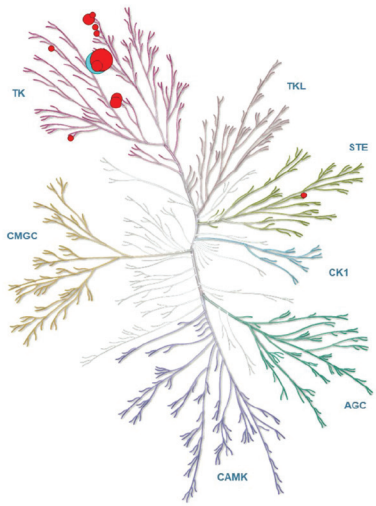
A preclinical kinase selectivity screen showed that NVL-655 is selective for ALK. Across a panel of 335 wild-type kinases, five kinases (ROS1, LTK, PYK2, TRKB, and FAK) are inhibited with $IC_{50} \leq$ 10-fold of ALK, and six other kinases are inhibited with $IC_{50} \leq$ 50-fold of ALK, as depicted by the red circles in Figure 19 below. Given the high selectivity of NVL-655 over TRKB in a more physiologically relevant context, as depicted in Figure 18 above, we believe the actual fold selectivity over TRKs may be even greater than demonstrated in the kinase selectivity screen. The vast majority of kinases (323 kinases) are inhibited with $IC_{50} >$ 50-fold of ALK and are not plotted.

Figure 19. Selectivity of NVL-655 for ALK over other kinases in a preclinical assay

SELECTIVITY INDEX Relative to ALK-wt	KINASE
≤ 1x	ALK, ROS1
1 – 10x	LTK, PYK2, TRKB*, FAK
10 – 50x	SLK, TRKA*, FER, MUSK, EPHA6, TRKC*
>50x	323 other kinases

*Due to limitations of this biochemical assay, the actual fold selectivity over TRKs may be greater than shown.

$$\text{Selectivity index} = \frac{IC_{50}\text{ (kinase of interest)}}{IC_{50}\text{ (ALK wild-type)}}$$

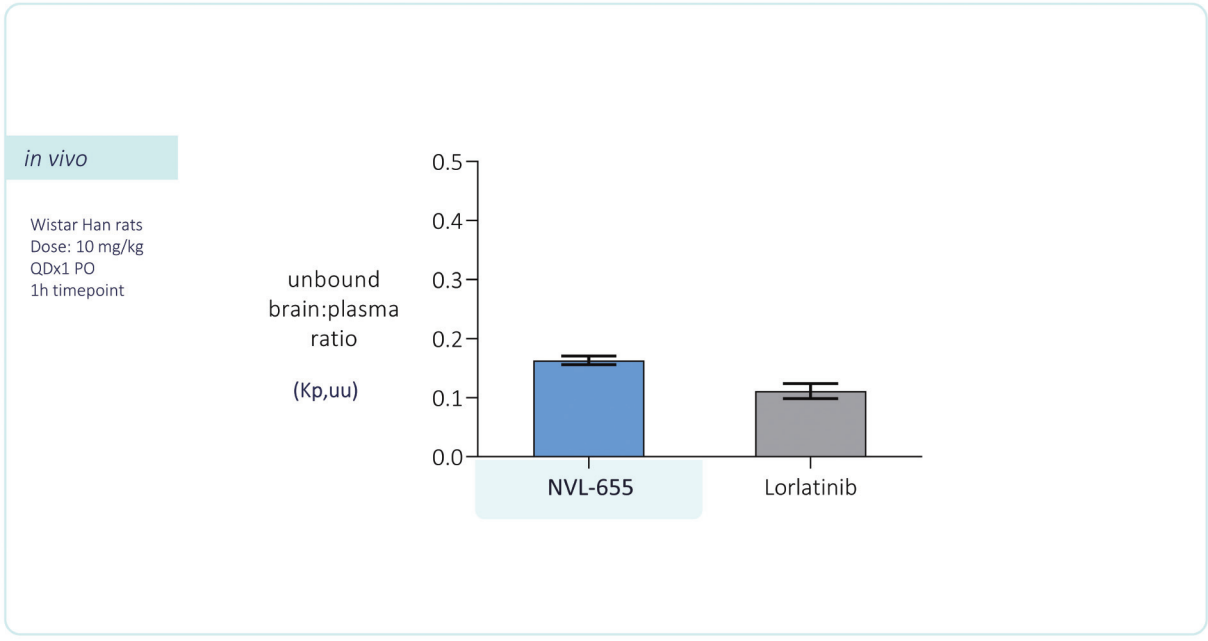


**Results of kinase selectivity screen for NVL-655 (Wild-Type Kinase Panel, Reaction Biology, Germany), displayed on a kinome tree. The panel includes 335 wild-type kinases. The selectivity index of NVL-655 for ALK wild-type versus all other tested kinases was calculated as IC_{50} of NVL-655 for the kinase of interest / IC_{50} of NVL-655 for ALK wild-type. For each kinase of interest, a selectivity index greater than 1 indicates that NVL-655 is selective for ALK over the other kinase. The size of the red circles corresponds to the selectivity index, or IC_{50} relative to ALK. Kinases with IC_{50} > 50-fold of ALK IC_{50} are not plotted. Due to limitations of this biochemical assay, the actual fold selectivity over TRKB may be greater than shown. The selectivity of NVL-655 for ALK wild-type and ALK resistance variants over TRKB was further characterized in a more physiologically relevant assay as presented in Figure 18 above.*

Optimized brain penetration

We conducted a pharmacokinetic experiment where the preclinical brain exposure of NVL-655 and lorlatinib, a highly brain-penetrant kinase inhibitor, was measured in parallel in rodents. NVL-655 and lorlatinib exhibited similar unbound brain-to-plasma ratio, as shown in Figure 20 below, suggesting that NVL-655 may have similarly high brain penetrance in patients. This experiment was not powered to determine the statistical significance of differences in Kp,uu for NVL-655 versus lorlatinib.

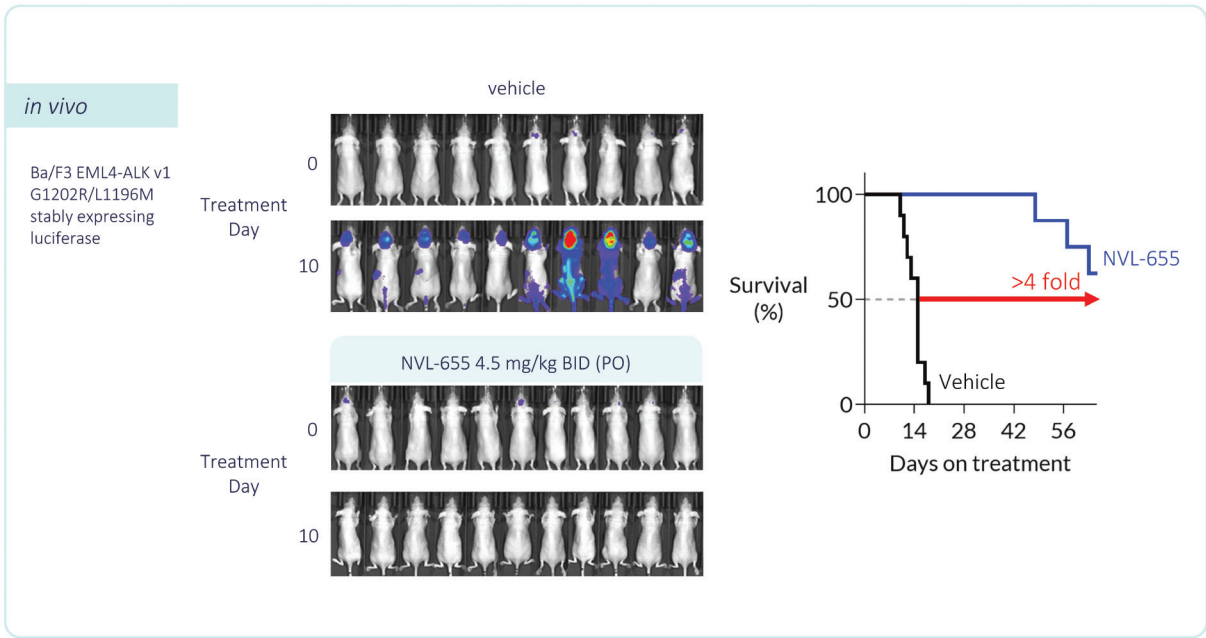
Figure 20. Preclinical brain penetrance of NVL-655 and CNS-active drug lorlatinib



**Wistar Han rats were administered a single oral dose (QDx1 PO) of 10 mg/kg NVL-655 or lorlatinib. After one hour, plasma and brain tissue were collected and analyzed to determine Kp,uu, a measure of brain penetration calculated as the ratio of unbound drug in the brain to unbound drug in the plasma outside of the brain. Average Kp,uu ± SEM is plotted (n=3). This experiment was not powered to determine the statistical significance of differences in Kp,uu for NVL-655 versus lorlatinib.*
No head-to-head clinical studies have been conducted for lorlatinib versus NVL-655. No clinical studies have been conducted for NVL-655.

In an *in vivo* mouse intracranial tumor model of Ba/F3 EML4-ALK v1 G1202R/L1196M luciferase, treatment with NVL-655 reduced brain tumors and demonstrated a significant extended median survival of more than four-fold compared to the vehicle ($p<0.0001$), as seen in Figure 21.

Figure 21. CNS anti-tumor activity of NVL-655 in an *in vivo* preclinical model



**(Left) Ba/F3 cells were engineered to express the EML4-ALK v1 fusion with the G1202R/L1196M compound resistance mutation, and luciferase to enable bioluminescence imaging. These cells were stereotactically implanted into the right forebrains of Balb/c nude mice. After five days, mice were randomized based on mean bioluminescence signal and treated orally BID with NVL-655 (4.5 mg/kg shown) or vehicle (20% HP-ß -CD). Images of tumor burden on day 10 following treatment initiation are shown, where color represents luminescence as an indicator of tumor burden on a color scale from blue = 4.00×10^6 (lower tumor burden) to red = 2.00×10^8 photons/sec/cm2/sr (higher tumor burden). (Right) A survival analysis from this same experiment is presented, with vehicle n=10 and NVL-655 n=7 (n=3 from the initial n=10 assigned to the NVL-655 dosing group were randomly removed from survival analysis for pharmacokinetic measurements). Number of mice per group was selected assuming signal/noise ratio of ≥ 1.4, 5% significance level, and 80% power versus vehicle. Median survival was 15 days for vehicle group and >65 days for the NVL-655-treated group, corresponding to a significant median overall survival extension >4-fold (P-value < 0.001, log-rank Mantel-Cox test).*
BID = dosing two times per day, PO = oral administration.

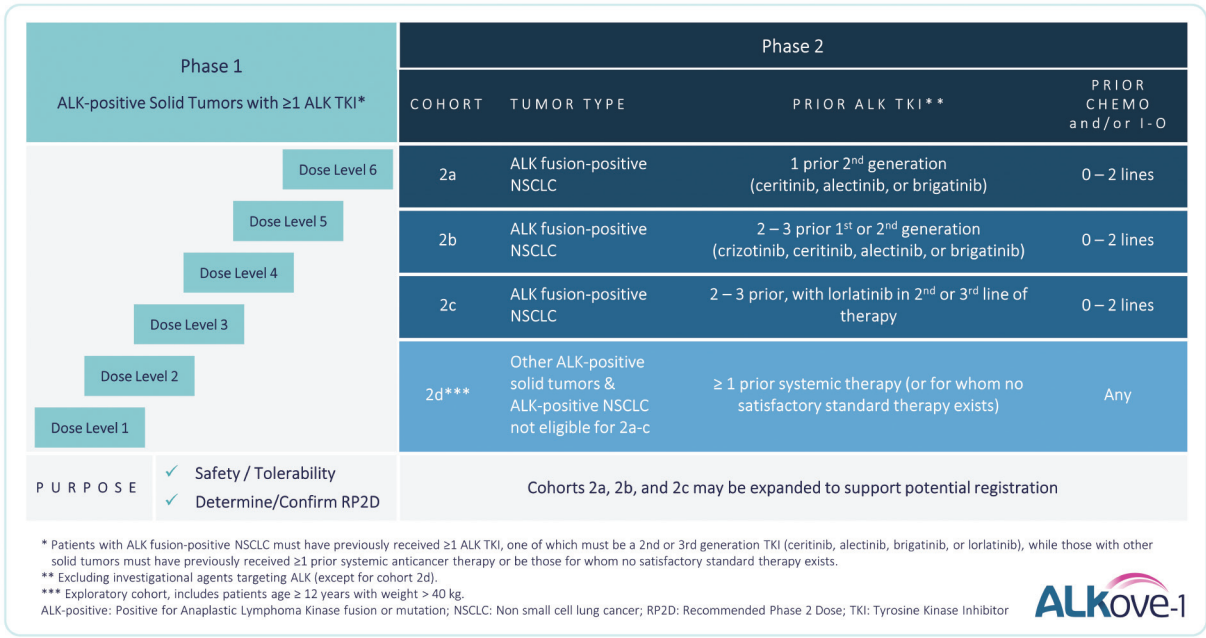
Clinical development plan: NVL-655

We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the Phase 1 portion of our planned ALKOVE-1 study, a first-in-human Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022. The planned study design is depicted in Figure 22 below.

The planned Phase 1 portion of the clinical trial is designed to evaluate the overall safety and tolerability of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors, as well as to determine the RP2D, characterize the pharmacokinetic profile, and evaluate preliminary anti-tumor activity of NVL-655. In this phase, we also plan to enroll adults with ALK-positive cancers with or without brain metastases.

The planned Phase 2 portion of the clinical trial is designed to evaluate the preliminary activity of NVL-655 at the RP2D in a limited number of patients with advanced ALK-positive NSCLC and other solid tumors, examining several specific cohorts of patients based on prior anti-cancer therapies they have received. The Phase 2 cohorts are designed with the intent to expand in size, as data emerge and in collaboration with FDA, into potentially registrational cohorts for the treatment of previously treated patients with ALK-positive NSCLC.

Figure 22. ALKOVE-1: Planned first-in-human clinical trial of NVL-655 in advanced ALK-positive NSCLC and other solid tumors



Based on the totality of clinical data from the Phase 1 portion of the clinical trial, and if supported by an acceptable safety profile, favorable pharmacokinetics and pharmacodynamics, and a positive efficacy signal in patients with ALK-positive cancers, we plan to engage with the FDA and other regulatory agencies to discuss our plans for the Phase 2 portion of the clinical trial, specifically to evaluate the safety and antitumor activity of NVL-655 at the RP2D and expand specific cohort sizes further into potentially registrational cohorts to address significant medical needs for patients with ALK-positive NSCLC.

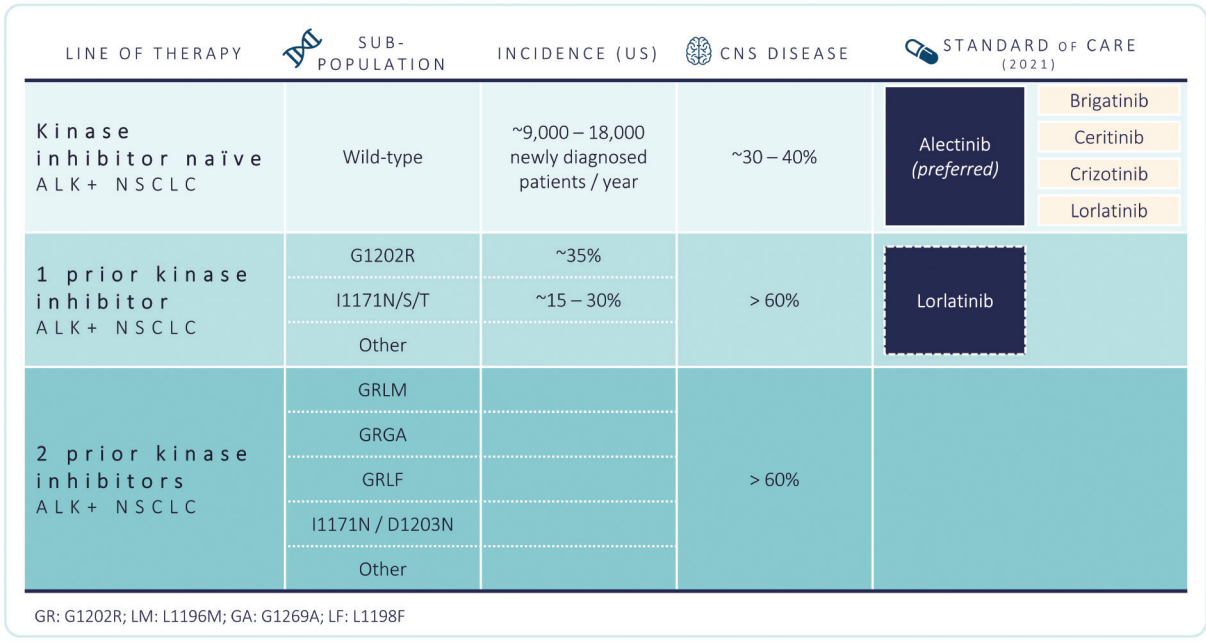
We plan to initially enroll the Phase 1 dose escalation portion of the clinical trial in the U.S. and in Europe, utilizing some of the leading cancer centers with experience in early phase studies with precision oncology medicines, while maintaining active engagement with leading clinical and translational thought leaders. Following the initial Phase 1 dose escalation portion of the clinical trial, we plan to further enroll the Phase 2 portion of the clinical trial in additional geographies. The Phase 2 portion of the clinical trial is intended to further evaluate the safety and preliminary antitumor activity of NVL-655 at the RP2D in a limited number of patients, with the potential to expand cohort sizes to support global marketing applications following discussions with global regulators.

The design of the Phase 1/2 clinical trial has been discussed with the FDA. Pending supportive data, we plan to engage with regulators about expedited drug development pathways, such as Fast Track designation, Breakthrough Therapy designation, Priority Review designation, and other collaborative mechanisms.

ALK market opportunity

There are approximately 9,000 to 18,000 newly diagnosed patients a year in the U.S. with ALK-positive NSCLC, representing up to 5% of all NSCLC patients. At the time of diagnosis, up to 40% of ALK-positive NSCLC patients present with accompanying brain metastases, requiring therapy with the ability to penetrate the BBB. Approximately 35% of patients who progress on kinase inhibitor therapy (alectinib or brigatinib) have the ALK G1202R mutation, representing a significant population in need of effective therapy. The ALK-positive NSCLC market overview is summarized in Figure 23 below.

Figure 23. ALK-positive NSCLC market overview



Data from the Phase 2 cohorts are intended to address significant medical needs for patients with ALK-positive NSCLC. We plan to engage global regulators early and frequently in development about the potential for this study to support global marketing applications. Beyond NSCLC, we believe that NVL-655 has the potential to treat pediatric and adult patients with ALK-positive cancer in other tumor types, such as lymphoma, inflammatory myofibroblastic, esophageal, renal, breast, colon, ovarian, and thyroid cancers.

Our discovery programs

Our approach has enabled us to identify product candidates for our parallel lead ROS1 and ALK programs in our first two years, in addition to launching multiple early-stage discovery programs that we expect to nominate two additional product candidates in 2022.

We continue to evaluate new program areas with a focus on addressing the limitations of existing therapies for other clinically proven kinase targets in oncology. As treatment landscapes evolve, we also continue to work with our physician-scientist partners to anticipate emerging patient needs in established areas of development and leverage our existing expertise in the area with the aim to efficiently discover and develop new product candidates with the potential to comprehensively address those emerging challenges. We believe that opportunities to apply our established model of efficient drug discovery and development are growing, and align with the increasing adoption of kinase inhibitors as standard of care across a broadening set of indications.

ALK IXDN

In addition to the ALK G1202R+ single and compound mutations discussed above, additional treatment emergent ALK resistance mutations are increasingly well characterized in ALK NSCLC patients. Following treatment with alectinib, various ALK I1171X mutations have been reported, where X = N, S, or T. Although patients with tumors harboring ALK I1171X mutations have responded to lorlatinib, many have subsequently further relapsed following emergence of ALK compound mutations such as I1171X/D1203N (collectively, IXDN). Current FDA approved ALK therapies do not have activity against IXDN mutations. In addition, we are not aware of any development compounds that have activity against IXDN and the potential to address this emerging medical need.

Our ALK IXDN program is designed to discover and develop a potent and brain-penetrant inhibitor of ALK, ALK I1171X, and IXDN. As with our NVL-655 program for ALK and ALK G1202R+ single and compound

mutations, this compound is designed to optimize for brain penetrance and selectivity over TRKB to minimize CNS adverse events. Our ALK IXDN program is in the discovery research phase and has been further accelerated by the expertise and prior candidate pool we have developed for selective inhibition of ALK. We expect to nominate a development candidate in 2022.

HER2 Exon 20 insertions

Mutations and alterations in HER2 are oncogenic and are found in approximately 3% of cancers, including up to 4% of advanced NSCLC patients. Within NSCLC, 90% of HER2 mutations occur through deletions, insertions, or duplications (collectively known as HER2 Exon 20 Insertions). HER2 mutations have also been identified in multiple cancers, including breast, esophageal, endometrial, bladder, colorectal, skin, ovarian, head and neck, and cervical.

No targeted agents are FDA approved specifically for cancers with HER2 Exon 20 Insertions, and standard of care is platinum-based chemotherapy. Existing HER2 small molecule therapies investigated in this population, including erlotinib, gefitinib, afatinib, dacomitinib, lapatinib, and neratinib, are also potent inhibitors of wild-type EGFR, which can lead to adverse events including skin rash and diarrhea. Adequate brain penetrance is another limitation for current therapies under investigation in this patient population, precluding robust responses in CNS involved disease. Retrospective studies have shown that 19% of HER2 mutant NSCLC patients present with brain metastases, and an additional 28% develop brain metastases during treatment, highlighting the importance for CNS active compounds in this patient population. A new therapy targeting mutant HER2 that is both (i) brain-penetrant to treat or prevent brain metastases, and (ii) can spare wild-type EGFR to limit EGFR-related adverse events and dose-limiting toxicities, may provide a preferred option for patients.

Our HER2 program seeks to identify a small molecule inhibitor of HER2 Exon 20 Insertions that has selectivity over EGFR and strong brain penetrance. This profile is designed to minimize potential wild-type EGFR-related toxicities and address the prevalence of brain metastases. Our HER2 program is in the discovery research phase and we expect to nominate a development candidate in 2022.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on proprietary products. While we believe that our technology, the expertise of our team, and our development experience and scientific knowledge provide us with competitive advantages, we face competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions, governmental agencies, and public and private research institutions. Product candidates that we successfully develop and commercialize may compete with existing therapies and new therapies that may become available in the future.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources, established presence in the market, and expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. Additional mergers and acquisitions may result in even more resources being concentrated in our competitors.

Our commercial potential could be reduced or eliminated if our competitors develop and commercialize products that are safer or more effective, have fewer or less severe adverse events, and are more convenient or less expensive than products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we can, which could result in our competitors establishing a strong market position before we are able to enter the market or could otherwise make our development more complicated. We believe the key competitive factors affecting the success of all of our programs are likely to be efficacy, including duration of response (DOR) and breadth of coverage, safety, and patient convenience.

We also face competition more broadly across the 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 and targeted drug therapy or a combination of 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 drug 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. We expect that if our product candidates are approved, they will be priced at a significant premium over competitive generic, including branded generic, 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 will pose challenges. In addition, many companies are developing new therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

There are currently two ROS1-targeted kinase inhibitor drugs approved for use in first-line, treatment-naïve ROS1-positive NSCLC: Pfizer's Xalkori (crizotinib) and Roche's Rozlytrek (entrectinib). Following treatment with these approved first-line therapies, mutations such as ROS1 G2032R have been observed to confer treatment resistance and limit durability of response. In addition, the ability of crizotinib to address brain metastases is limited by its ability to penetrate the BBB. While entrectinib is better able to penetrate the brain, CNS adverse events have been observed that are consistent with potential off-target inhibition of TRK in the CNS. Pfizer's lorlatinib is a dual ALK/ROS1 inhibitor that is in development for the treatment of ROS1-positive NSCLC. This product has received marketing approval for the treatment of ALK-positive NSCLC under the trade name Lorbrena and has demonstrated CNS activity as reported in its prescribing information. Novartis' Zykadia (ceritinib) is also recommended for use in ROS1-positive NSCLC patients, according to National Comprehensive Cancer Network (NCCN) guidelines. Turning Point Therapeutics, Inc.'s repotrectinib is a dual TRK/ROS1 inhibitor that is in development. This product has demonstrated clinical activity in ROS1-positive NSCLC patients but also retains potent TRK inhibition at clinically relevant concentrations. AnHeart Therapeutics' taletrectinib is a dual TRK/ROS1 inhibitor and is in development for patients with ROS1-positive NSCLC. As of February 28, 2022, there are no approved therapies for second-line treatment of ROS1-positive NSCLC, including for GR mutations. NVL-520 has a differentiated preclinical profile versus the approved and investigational ROS1 inhibitors as demonstrated by its potential to inhibit wild-type ROS1, inhibit ROS1 resistance mutations including ROS1 G2032R, penetrate the brain to address brain metastases, and avoid inhibition of TRK and other kinases to limit off-target side effects in the brain and in the periphery.

There are five currently approved ALK inhibitors for the treatment of NSCLC: Pfizer's Xalkori (crizotinib) and Lorbrena (lorlatinib), Novartis' Zykadia (ceritinib), Chugai/Roche's Alecensa (alectinib), and Takeda's Alunbrig (brigatinib). All five have now received full marketing approvals from the FDA for the line-agnostic treatment of ALK-positive NSCLC patients including for treatment-naïve patients as a first-line therapy. Crizotinib was the first FDA approved ALK inhibitor, receiving accelerated (conditional) approval for late stage ALK-positive NSCLC based on two single arm studies and the surrogate efficacy endpoints of objective response rate (ORR), and DOR. The FDA subsequently granted a line-agnostic indication based on two randomized studies of crizotinib versus chemotherapy in an untreated ALK-positive NSCLC patient population and in patients with ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen. The primary efficacy outcomes for these two studies were reported using the endpoint of progression free survival (PFS), supported by ORR, DOR, and overall survival (OS). The other four approved ALK inhibitors originally demonstrated safety and efficacy as measured by the surrogate endpoints of ORR and DOR in a second-line setting in support of an accelerated (conditional) approval. The FDA subsequently granted full and expanded approvals for a line-agnostic indication following completion of randomized studies in a front-line setting versus chemotherapy or crizotinib, with efficacy primarily measured using the endpoint of PFS and supported by ORR, DOR, and OS. The FDA has not made a conclusion regarding the relative safety and efficacy of these agents for the treatment of ALK-positive NSCLC patients. Emergent mutations such as ALK G1202R have been observed to confer treatment resistance and limit durability of response to crizotinib, ceritinib, alectinib, and brigatinib. Lorlatinib

has demonstrated activity in patients that have progressed on crizotinib, ceritinib, or alectinib. However, new compound mutations (e.g., GRLM and GRGA) have been reported in peer reviewed publications following sequential treatment with lorlatinib following another ALK inhibitor, limiting the durability of response to Lorbrena. The other four approved ALK inhibitors have not been shown to be clinically active against the G1202R single or compound mutations. Based upon clinical trials conducted by the sponsor, CNS activity has been reported in the FDA approved prescribing information for ceritinib, alectinib, brigatinib, and lorlatinib. Based upon clinical trials conducted by the sponsor, CNS adverse events have been reported in the FDA approved prescribing information for lorlatinib that are consistent with potential off-target inhibition of TRK in the CNS. NVL-655 has a differentiated preclinical profile demonstrated by its potential to selectivity inhibit ALK and ALK mutant variants as compared to TRK, and ability to penetrate the brain. In particular, it retains activity against ALK compound mutations GRLM, GRGA, and GRLF for which there are no available treatment options.

Revenue Sharing Agreements

Revenue Sharing Agreement with Deerfield

We are party to an Amended and Restated Revenue Sharing Agreement with Deerfield Healthcare Innovations Fund, L.P. and Deerfield Private Design Fund, IV, L.P. (collectively, Deerfield) pursuant to which we are obligated to pay Deerfield a low single digit percentage of net sales of any commercial products discovered, identified or generated by the Company during the period commencing on February 2, 2017 and ending on the date that is the earlier of (i) five years after Deerfield's last investment in our capital stock and (ii) the fifth anniversary of our initial public offering (IPO). Any payments in respect of such products would be through the later of 12 years from the first commercial sale in a country or the expiration of the last-to-expire patent in that country. To date, we have not made any payments under this agreement and there are no upfront fees or milestone payments required to be paid by us under this agreement. We have not yet obtained or exclusively in-licensed any issued patents, and all of the patent applications that we own are at a very early stage of prosecution. Any U.S. and foreign patents that may issue based on our pending Patent Cooperation Treaty (PCT) and U.S. applications for our ROS1 and ALK programs are expected to expire no earlier than 2041, without giving effect to any patent term adjustments, patent term extensions that may be awarded, or additional patents that may be filed. We also have no products approved for commercial sale and have not generated any revenue.

Revenue Sharing Agreements with our scientific founder

We are party to an Amended and Restated Revenue Sharing Agreement with our scientific founder and director, Matthew Shair, Ph.D., pursuant to which we are obligated to pay Dr. Shair a low single digit percentage of net sales of certain commercial products that either have a mechanism of action of (i) ROS1 inhibition and contain NVL-520 or a backup compound substituted therefore in the event of a product development failure or (ii) ALK inhibition and contain NVL-655 or a backup compound substituted therefore in the event of a product development failure, in each case through the later of 12 years from the first commercial sale in a country or the expiration of the last-to-expire patent in that country. To date, we have not made any payments under this agreement and there are no upfront fees or milestone payments required to be paid by us under this agreement. We have not yet obtained or exclusively in-licensed any issued patents, and all of the patent applications that we own are at a very early stage of prosecution. Any U.S. and foreign patents that may issue based on our pending PCT and U.S. applications for our ROS1 and ALK programs are expected to expire no earlier than 2041, without giving effect to any patent term adjustments or patent term extensions that may be awarded or additional patents that may be filed. We also have no products approved for commercial sale and have not generated any revenue.

Intellectual property

Our commercial success depends in part on our ability (i) to obtain and maintain patent and other proprietary and/or intellectual property rights and protection for our technology, inventions, and improvements; (ii) to protect and preserve the confidentiality of our trade secrets; (iii) to defend and enforce our proprietary and intellectual property rights, including any patents that we may own or license in the future; and (iv) to operate without infringing the valid and enforceable patents and other proprietary and/or intellectual property rights of third parties.

We wholly own PCT applications, U.S. patent applications and U.S. provisional patent applications relating to our lead and planned product candidates. We strive to protect our proprietary position by, among other methods, filing patent applications in the U.S. and in jurisdictions outside of the U.S. directed to our proprietary technology, inventions, improvements, and product candidates that are important to the development and implementation of our business. We also rely on trade secrets and know-how relating to our proprietary technology and product candidates and continuing innovation to develop, strengthen and maintain our proprietary position in the field of oncology. Our strategic plans also include reliance on data exclusivity, market exclusivity, and patent term extensions when available.

Our ability to stop third parties from making, using, selling, offering to sell, or importing products identical or similar to ours will depend on the extent to which we have rights under valid and enforceable patents, trade secrets, or other intellectual property rights that cover these activities. The patent rights of biotechnology and pharmaceutical companies like ours are generally uncertain and can involve complex legal, scientific, and factual issues. Our and any future licensor's current and future patent applications may not result in the issuance of any patent in any particular jurisdiction, and the claims of any current or future issued patents, even if those claims are valid and enforceable, may not provide sufficient protection from competitors. Any owned or in-licensed patent rights we may obtain may not enable us to prevent others from replicating, manufacturing, using, or administering our product candidates for any indication. Moreover, the subject matter initially claimed in a patent application may be significantly reduced before a patent is issued, and a patent's scope can be reinterpreted after issuance. In addition, any patent we may own or in-license may be challenged, circumvented or invalidated by third parties. As a result, we cannot ensure that any of our product candidates will be protected by valid and enforceable patents. See "Risk factors—Risks related to our intellectual property" for a more comprehensive description of risks related to our intellectual property.

We have filed certain patent applications directed generally to compositions of matter, pharmaceutical formulations, and therapeutic methods of using the foregoing related to our ROS1, ALK, HER2, and ALK IXDN programs, as summarized below. We also possess substantial know-how and trade secrets relating to the development and commercialization of our product candidates, including related manufacturing processes and technology. In addition, we own certain pending U.S. trademark applications.

With respect to our ROS1 program, we own a pending PCT patent application, a pending U.S. patent application and two pending U.S. provisional patent applications directed to our ROS1 inhibitory compounds (*e.g.,* NVL-520) and methods of use of such compounds. Any U.S. and foreign patents that may issue based on the PCT or U.S. applications are expected to expire no earlier than 2041, not including any patent term adjustments or patent term extensions that may be awarded. With respect to our ALK program, we own a pending PCT patent application and a pending U.S. patent application directed to our ALK inhibitory compounds (*e.g.,* NVL-655) and methods of use of such compounds. Any U.S. and foreign patents that may issue based on the PCT or U.S. application are expected to expire no earlier than 2041, not including any patent term adjustments or patent term extensions that may be awarded. With respect to our HER2 program, we own several pending U.S. provisional patent applications. Any U.S. and foreign patents that may issue based on these applications are expected to expire no earlier than 2042, not including any patent term adjustments or patent term extensions that may be awarded. With respect to our ALK IXDN program, we own a pending PCT application and a pending U.S. provisional patent application. Any U.S. and foreign patents that may issue based on these applications are expected to expire no earlier than 2042, not including any patent term adjustments or patent term extensions that may be awarded. In addition, we expect to file additional patent applications related to each of these programs.

Our pending and planned applications may not result in issued patents and we cannot provide any assurance that any patents that might issue in the future will protect our future products or provide us with any competitive advantage. Moreover, U.S. provisional patent applications are not eligible to become issued patents until, among other things, we file a non-provisional patent application within 12 months of the filing of the related provisional patent applications. With regard to our provisional patent applications, if we do not timely file one or more non-provisional patent applications, we may lose our priority date with respect to our provisional patent applications and therefore any patent protection on the inventions disclosed in such provisional patent applications. While we intend to timely file one or more non-provisional patent applications relating to our

provisional patent applications, we cannot predict whether any such patent applications will result in the issuance of patent(s) that provide us with any competitive advantage. For more information regarding the risks related to our intellectual property, please see "Risk Factors—Risks Related to Our Intellectual Property."

Commercialization

We intend to retain significant development and commercial rights to our product candidates and, if marketing approval is obtained, to commercialize our product candidates on our own, or potentially with a collaboration partner, in the U.S. and other regions. We currently have no sales, marketing, or commercial product distribution capabilities. We intend to build the necessary infrastructure and capabilities over time for the U.S., and potentially other regions, following further advancement of our product candidates. We believe that such a focused sales and marketing organization will be able to address the community of oncologists who are the key specialists in treating the patient populations for which our product candidates are being developed. Clinical data, the size of the addressable patient population, and the size of the commercial infrastructure and manufacturing needs may all influence or alter our commercialization plans. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Manufacturing

We do not own or operate, and currently have no plans to establish, 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, as well as for commercial manufacturing if any of our product candidates obtain marketing approval. We also rely, and expect to continue to rely, on third parties to package, label, store and distribute our investigational product candidates, as well as our commercial products if marketing approval is obtained.

We believe that this strategy allows us to maintain a more efficient infrastructure by eliminating the need for us to invest in our own manufacturing facilities, equipment, and personnel while also enabling us to focus our expertise and resources on the development of our product candidates.

All of our product candidates are small molecules and are manufactured in synthetic processes from available starting materials. The chemistry appears amenable to scale-up and does not currently require unusual equipment in the manufacturing process. We expect to continue to develop product candidates that can be produced cost-effectively at contract manufacturing facilities.

Currently, active pharmaceutical ingredients (API) (*i.e.*, clinical drug substance) for NVL-520 and NVL-655 are manufactured in accordance with current good manufacturing practices (cGMPs).

The drug product formulation is being developed with the goal of producing tablets with consistent and immediate release dissolution profiles that can be reproducibly manufactured using automated equipment. All manufacturing activities for NVL-520 and NVL-655 drug products are performed in accordance with cGMPs. We currently rely on these vendors as single-source contract manufacturing organizations.

We are in the process of developing our supply chain for each of our product candidates and intend to put in place framework agreements under which third-party contract manufacturing organizations (CMOs) will generally provide us with necessary quantities of API and drug product on a project-by-project basis based on our development needs.

As we advance our product candidates through development, we will explore adding backup suppliers for the API and drug product for each of our product candidates to protect against any potential supply disruptions.

We generally expect to rely on third parties for the manufacture of any companion diagnostics we may develop.

However, there are no assurances that our manufacturing and supply chain infrastructure will remain uninterrupted and reliable, or that the third parties we rely on will be able to satisfy our demand in a timely manner and not have supply chain disruptions due to COVID-19 related shutdowns, stock-outs due to raw material shortages and/or greater than anticipated demand or quality issues given the operational challenges and raw material shortages that have been experienced during the COVID-19 pandemic.

Government regulation

The research, development, testing, manufacture, quality control, packaging, labeling, storage, record-keeping, distribution, import, export, promotion, advertising, marketing, sale, pricing and reimbursement of drug products are extensively regulated by governmental authorities in the U.S. and other countries. The processes for obtaining regulatory approvals in the U.S. and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory requirements, both pre-approval and post-approval, require the expenditure of substantial time and financial resources. The regulatory requirements applicable to drug product development, approval and marketing are subject to change, and regulations and administrative guidance often are revised or reinterpreted by the agencies in ways that may have a significant impact on our business.

U.S. Government Regulation of Drug Products

In the U.S., the FDA approves and regulates human drugs under the Federal Food, Drug, and Cosmetic Act (FDCA). A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products is typically referred to as a sponsor. The failure of a sponsor to comply with applicable U.S. requirements may result in FDA delays or refusal to approve pending New Drug Applications (NDAs), and may subject the sponsor to administrative or judicial sanctions, such as issuance of warning letters, or the imposition of fines, civil penalties, product recalls, product seizures, total or partial suspension of production or distribution, injunctions and/or civil or criminal prosecution brought by the FDA and the U.S. Department of Justice or other governmental entities.

The FDA must approve our product candidates for therapeutic indications before they may be marketed in the U.S. A sponsor seeking approval to market and distribute a new drug product in the U.S. must satisfactorily complete each of the following steps:

- completion of preclinical laboratory tests, animal studies and formulation studies according to good laboratory practices (GLP) regulations or other applicable regulations;
- design of a clinical protocol and submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be updated when certain changes are made;
- approval by an independent institutional review board (IRB) or ethics committee representing each clinical trial site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, good clinical practices (GCPs) and other clinical-trial related regulations to evaluate the safety and efficacy of the investigational product for each proposed indication;
- preparation and submission to the FDA of an NDA requesting marketing approval for one or more proposed indications, including payment of application user fees;
- review of the NDA by an FDA advisory committee, where applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the drug is produced to assess compliance with cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality, and purity;
- satisfactory completion of any FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data submitted in support of the NDA; and
- FDA review and approval of the NDA, which may be subject to additional post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy (REMS), and any post-approval studies required by the FDA.

Preclinical Studies

Before a sponsor begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product

chemistry, formulation, and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards and the U.S. Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. An IND must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial may proceed. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

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

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

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

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board (DSMB). This group provides authorization as to whether or

not a trial may move forward at designated checkpoints based on review of available data from the study, to which only the DSMB maintains access. Suspension or termination of development during any phase of a clinical trial can occur if the DSMB determines that the participants or patients are being exposed to an unacceptable health risk.

Expanded Access

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

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

There is no obligation for a sponsor to make its investigational products available for expanded access; however, as required by amendments to the FDCA included in the 21st Century Cures Act (the Cures Act), passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests with respect to product candidates in development to treat serious diseases or conditions, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study for a covered investigational product; or 15 days after the investigational product receives designation from the FDA as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

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

Human Clinical Trials

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements which include, among other things, the requirement that all research subjects provide their informed consent in writing before they participate in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol, and any subsequent material amendment to the protocol, must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually.

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

- *Phase 1* clinical trials are initially conducted in a limited population, which may be healthy volunteers or subjects with the target disease, to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion, and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the product candidate's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.
- *Phase 2* clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are typically well-controlled and closely monitored.
- *Phase 3* clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken using a larger patient population to further evaluate dosage, provide substantial evidence of clinical efficacy, and further test for safety in an expanded and diverse patient population at multiple geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a new prescription drug product. Such Phase 3 clinical trials are referred to as "pivotal" trials.

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

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials, typically referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials, such as to verify clinical benefit in the case of products approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting mandatory Phase 4 clinical trials could result in withdrawal of FDA approval for products.

In August 2018, the FDA released a draft guidance entitled "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics," which outlines how developers can utilize an adaptive trial design commonly referred to as a seamless trial design in early stages of oncology product development (i.e., the first-in-human clinical trial) to compress the traditional three phases of trials into one continuous trial called an expansion cohort trial. Information to support the design of individual expansion cohorts are included in IND applications and assessed by the FDA. Expansion cohort trials can potentially bring efficiency to product development and reduce developmental costs and time.

Typically, clinical trials are designed in consultation with the FDA or foreign regulatory authorities during these development phases. The indications under development can influence the study designs employed during the conduct of clinical trials, such as for a first-line cancer treatment indication which may require head-to-head comparison data demonstrating clinical superiority or non-inferiority to currently available therapies. The

timeline for first-line cancer indication development programs may also be longer than for indications sought in subsequent or later lines of treatment due to a desire for regulatory authorities to expedite access to treatments for patients whose cancer has progressed on prior treatments and in settings where there may be no available therapy option. As such, many new oncology products initially seek an indication for second or third-line treatment, which may be a smaller available treatment population in any oncology indication that has limited or no other therapy options, with subsequent development sought for those products in earlier front lines of treatment which target a larger treatment population and may require the conduct of additional clinical trials to provide comparative data against an available therapy option to show clinical superiority.

In response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and has updated it periodically since that time, to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (*e.g.,* participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study, among other things. The FDA has indicated that it will continue to provide any necessary guidance to sponsors, clinical investigators, and research institutions as the public health emergency evolves. In June 2020 the FDA also issued a guidance on good manufacturing practice considerations for responding to COVID-19 infection in employees in drug products manufacturing, including recommendations for manufacturing controls to prevent contamination of drugs.

Reporting Clinical Trial Results

Sponsors of clinical trials of certain FDA-regulated products, including prescription drugs, are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the U.S. National Institutes of Health (NIH). In particular, information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Although sponsors are also obligated to disclose the results of their clinical trials after completion, disclosure of the results can be delayed in some cases for up to two years after the date of completion of the trial. The NIH's Final Rule on registration and reporting requirements for clinical trials became effective in 2017, and both the NIH and the FDA have recently signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors.

Specifically, the Secretary of Health and Human Services (HHS) is authorized to issue a notice of noncompliance to a responsible party for failure to submit clinical trial information as required. The responsible party, however, is allowed 30 days to correct the noncompliance and submit the required information. The failure to submit clinical trial information to clinicaltrials.gov, as required, is also a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. In addition to civil monetary penalties, violations may also result in other regulatory action, such as injunction and/or criminal prosecution or disqualification from federal grants. Although the FDA has historically not enforced these reporting requirements due to HHS's long delay in issuing final implementing regulations, those regulations have now been issued and the FDA did issue its first Notice of Noncompliance to a manufacturer in April 2021.

Interactions with the FDA During the Clinical Development Program

Following the clearance of an IND and the commencement of clinical trials, the sponsor will continue to have interactions with the FDA. Progress reports detailing the results of clinical trials must be submitted annually within 60 days of the anniversary dates that the IND went into effect and more frequently if serious adverse events occur. These reports must include a development safety update report. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that

listed in the protocol or investigator brochure. Phase 1, Phase 2, and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In addition, sponsors are given opportunities to meet with the FDA at certain points in the clinical development program. Specifically, sponsors may meet with the FDA prior to the submission of an IND (Pre-IND meeting), at the end of Phase 2 clinical trial (EOP2 meeting) and before an NDA is submitted (Pre-NDA meeting). Meetings at other times may also be requested. There are three types of meetings that occur between sponsors and the FDA. Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND and pre-NDA meetings as well as end of phase meetings such as EOP2 meetings. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product, including for example meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use.

These meetings provide an opportunity for the sponsor to share information about the data gathered to date with the FDA and for the FDA to provide advice on the next phase of development. For example, at an EOP2 meeting, a sponsor may discuss its Phase 2 clinical results and present its plans for the pivotal Phase 3 clinical trial(s) that it believes will support the approval of the new product. Such meetings may be conducted in person, via teleconference/videoconference, or written response only with minutes reflecting the questions that the sponsor posed to the FDA and the agency's responses. The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure.

Manufacturing and Other Regulatory Requirements

Concurrently with clinical trials, sponsors usually complete additional animal safety studies, develop additional information about the chemistry and physical characteristics of the product candidate, and finalize a process for manufacturing commercial quantities of the product candidate in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other criteria, the sponsor must develop methods for testing the identity, strength, quality, and purity of the finished product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Specifically, the FDA's regulations require that pharmaceutical products be manufactured in specific approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports, and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies, and they are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. The FDA's regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the sponsor and any third-party manufacturers involved in producing the approved product.

Pediatric Studies

Under the Pediatric Research Equity Act (PREA), applications and certain types of supplements to applications must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor must submit an initial Pediatric Study Plan (PSP) within 60 days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The sponsor and the FDA must reach agreement on a final plan. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

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

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law now requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension, or have failed to request approval for a required pediatric formulation. It further requires the FDA to publicly post the PREA Non-Compliance letter and sponsor's response. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA also maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population.

Expedited Review Programs

For certain drug products, the FDA is authorized to expedite the review and approval of applications in several ways. None of these expedited programs changes the standards for approval, but they may help expedite the development and approval process governing product candidates.

- *Fast Track designation*. Candidate products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening *condition* and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with the FDA, the FDA may initiate review of sections of a Fast Track application before the application is complete, a process known as rolling review.
- *Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient development program,

intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.

- *Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention compared to marketed products. The FDA aims to complete its review of priority review applications within 6 months as opposed to 10 months for standard review.
- *Accelerated approval.* Drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.
- *Regenerative advanced therapy.* With passage of the Cures Act in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review, and accelerated approval based on surrogate or intermediate endpoints.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the sponsor to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Section 505(b)(2) thus authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved as well as for any new indication sought by the Section 505(b)(2) applicant.

Submission and Filing of NDAs

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product's chemistry, manufacturing, controls, safety updates, patent information, abuse information, and proposed labeling, are submitted to the FDA as part of an application

requesting approval to market the product candidate for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of a drug product to the satisfaction of the FDA. The fee required for the submission and review of an application under the Prescription Drug User Fee Act (PDUFA) is substantial (for example, for fiscal year 2022, this application fee is approximately $3.1 million), and the sponsor of an approved application is also subject to an annual program fee, currently more than $369,000 per eligible prescription product. These fees are typically adjusted annually, and exemptions and waivers may be available under certain circumstances, such as where a waiver is necessary to protect the public health, where the fee would present a significant barrier to innovation, or where the sponsor is a small business submitting its first human therapeutic application for review.

The FDA conducts a preliminary review of all applications within 60 days of receipt and must inform the sponsor at that time or before whether an application is sufficiently complete to permit substantive review. In pertinent part, the FDA's regulations state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File (RTF) determination to the applicant. Typically, an RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information, or analyses needed to evaluate safety and efficacy or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept an application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

After the submission is accepted for filing, the FDA begins an in-depth substantive review of the application. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile, and whether the product is being manufactured in accordance with cGMP. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application that is a new molecular entity, and six months from the filing date for an application with "priority review." The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission. Despite these review goals, it is not uncommon for FDA review of an application to extend beyond the PDUFA goal date.

In connection with its review of an application, the FDA will typically submit information requests to the sponsor and set deadlines for responses thereto. The FDA will also conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether the manufacturing processes and facilities comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and are adequate to assure consistent production of the product within required specifications. The FDA also may inspect the sponsor and one or more clinical trial sites to assure compliance with IND and GCP requirements and the integrity of the clinical data submitted to the FDA. To ensure cGMP and GCP compliance by its employees and third-party contractors, a sponsor may incur significant expenditure of time, money, and effort in the areas of training, record keeping, production, and quality control.

Additionally, the FDA may refer an application, including applications for novel product candidates which present difficult questions of safety or efficacy, to an advisory committee for review, evaluation, and recommendation as to whether the application should be approved and under what conditions. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates, and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. Data from clinical trials are not always conclusive,

and the FDA or its advisory committee may interpret data differently than the sponsor interprets the same data. The FDA may also re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the sponsor during the review process.

The FDA also may require submission of a REMS if it determines that a REMS is necessary to ensure that the benefits of the product outweigh its risks and to assure the safe use of the product. The REMS could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. The FDA determines the requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS is needed, the sponsor of the application must submit a proposed REMS and the FDA will not approve the application without a REMS.

Decisions on NDAs

The FDA reviews an application to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The term "substantial evidence" is defined under the FDCA as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the product involved, on the basis of which it could fairly and responsibly be concluded by such experts that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical investigations to establish effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard. This approach was subsequently endorsed by Congress in 1998 with legislation providing, in pertinent part, that "If [the FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence." This modification to the law recognized the potential for the FDA to find that one adequate and well controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. In December 2019 the FDA issued draft guidance further explaining the studies that are needed to establish substantial evidence of effectiveness. It has not yet finalized that guidance.

After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA will issue either a Complete Response Letter (CRL) or an approval letter. To reach this determination, the FDA must determine that the drug is effective and that its expected benefits outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the NDA. This assessment is also informed by other factors, including: the severity of the underlying condition and how well patients' medical needs are addressed by currently available therapies; uncertainty about how the premarket clinical trial evidence will extrapolate to real-world use of the product in the post-market setting; and whether risk management tools are necessary to manage specific risks. In connection with this assessment, the FDA review team will assemble all individual reviews and other documents into an "action package," which becomes the record for FDA review. The review team then issues a recommendation, and a senior FDA official makes a decision.

A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, preclinical studies, or manufacturing. If a CRL is issued, the sponsor will have one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six month extension to respond.

The FDA has committed to reviewing resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. The FDA has taken the position that a CRL is not final agency action making the determination subject to judicial review.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. That is, the approval will be limited to the conditions of use (*e.g.,* patient population, indication) described in the FDA-approved labeling. Further, depending on the specific risk(s) to be addressed, the FDA may require that contraindications, warnings, or precautions be included in the product labeling, require that post-approval trials, including Phase 4 clinical trials, be conducted to further assess a product's safety after approval, require testing and surveillance programs to monitor the product after commercialization or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing trials or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

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

Post-approval Requirements

Following approval of a new prescription product, the manufacturer, the approved product, and the product's manufacturing locations are subject to pervasive and continuing regulation by the FDA, governing, among other things, monitoring and record-keeping activities, reporting of adverse experiences with the product and product problems to the FDA, product sampling and distribution, manufacturing, and promotion and advertising. Although physicians may prescribe legally available products for unapproved uses or patient populations (*i.e.,* "off-label uses"), manufacturers may not market or promote such uses. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. In September 2021 the FDA published final regulations that describe the types of evidence that the FDA will consider in determining the intended use of a drug product.

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

Further, if there are any modifications to the product, including changes in indications, labeling, or manufacturing processes or facilities, the sponsor may be required to submit and obtain FDA approval of a new application or supplement, which may require the sponsor to develop additional data or conduct additional preclinical studies and clinical trials. Securing FDA approval for new indications is similar to the process for approval of the original indication and requires, among other things, submitting data from adequate and well-controlled clinical trials to demonstrate the product's safety and efficacy in the new indication. Even if such trials are conducted, the FDA may not approve any expansion of the labeled indications for use in a timely fashion, or at all. There also are continuing, annual user fee requirements that are now assessed as program fees for certain products.

In addition, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information, imposition of post-market clinical trials requirement to assess new safety risks or imposition of distribution or other restrictions under a REMS program.

Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about a product;
- mandated modification of promotional materials and labeling and issuance of corrective information;
- fines, warning letters, untitled letters, or other enforcement-related letters or clinical holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- injunctions or the imposition of civil or criminal penalties; and
- consent decrees, corporate integrity agreements, debarment, or exclusion from federal health care programs.

In addition, the distribution of prescription pharmaceutical products is subject to a variety of federal and state laws, the most recent of which is still in the process of being phased into the U.S. supply chain and regulatory framework. The Prescription Drug Marketing Act (PDMA) was the first federal law to set minimum standards for the registration and regulation of drug distributors by the states and to regulate the distribution of drug samples. Today, both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. Congress more recently enacted the Drug Supply Chain Security Act (DSCSA), which made significant amendments to the FDCA, including by replacing certain provisions from the PDMA pertaining to wholesale distribution of prescription drugs with a more comprehensive statutory scheme. The DSCSA now requires uniform national standards for wholesale distribution and, for the first time, for third-party logistics providers; it also provides for preemption of certain state laws in the areas of licensure and prescription drug traceability.

Generic Drugs and Regulatory Exclusivity

In 1984, with passage of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs and it also enacted Section 505(b)(2). To obtain approval of a generic drug, a sponsor must submit an abbreviated new drug application (ANDA) to the FDA. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing conducted for a drug product previously approved under an NDA, known as the reference listed drug (RLD).

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug, and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA or 505(b)(2) application until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity (NCE). For the purposes of this provision, the FDA has consistently taken the position that an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. This interpretation was confirmed with enactment of the Ensuring Innovation Act in April 2021. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, a generic or follow-on drug application may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as new indications, dosage forms, route of administration or combination of ingredients. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs or 505(b)(2) NDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product; rather, this three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving follow-on applications for drugs containing the original active ingredient.

Five-year and three-year exclusivity also will not delay the submission or approval of a traditional NDA filed under Section 505(b)(1) of the FDCA; however, a sponsor submitting a traditional NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

As part of the submission of an NDA or certain supplemental applications, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Upon approval of a new drug, each of the patents listed in the application for the drug is then published in the Orange Book. The FDA's regulations governing patient listings were largely codified into law with enactment of the Orange Book Modernization Act in January 2021. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book. Specifically, the ANDA applicant must certify that: (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. Moreover, to the extent that the Section 505(b)(2) NDA applicant is relying on studies conducted for an already approved product, the applicant also is required to certify to the FDA concerning any patents listed for the NDA-approved product in the Orange Book to the same extent that an ANDA applicant would.

If the generic drug or follow-on drug applicant does not challenge the innovator's listed patents, the FDA will not approve the ANDA or 505(b)(2) application until all the listed patents claiming the referenced product have expired. A certification that the new generic product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. 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 owner and patent holders once the ANDA has been accepted for filing by the FDA. The NDA owner and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earliest of 30 months after the receipt of the Paragraph IV notice, expiration of the patent and a decision in the infringement case that is favorable to the ANDA or 505(b)(2) NDA applicant.

Orphan Drug Designation and Exclusivity

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

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

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first approved product. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

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

The period of market exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the disease or condition for which the product has been designated. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drug products that received orphan drug designation before enactment of amendments to the FDCA in 2017 but have not yet been approved by the FDA.

In September 2021 the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." It is unclear how this court decision will be implemented by the FDA.

Pediatric Exclusivity

Pediatric exclusivity is a type of non-patent marketing exclusivity in the U.S. and, if granted, provides for the attachment of an additional six months of exclusivity to the term of any existing patent or regulatory exclusivity, including the orphan exclusivity and regulatory exclusivities available under the Hatch-Waxman provisions of the FDCA. The conditions for pediatric exclusivity include the FDA's determination that information relating to the use of a new product in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric clinical trials, and the sponsor agreeing to perform, and reporting on, the

requested clinical trials within the statutory timeframe. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patents that cover the product are extended by six months. Although this is not a patent term extension, it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

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

Companion Diagnostics

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

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

In April 2020 the FDA issued additional guidance which describes considerations for the development and labeling of companion diagnostic devices to support the indicated uses of multiple drug or biological oncology products, when appropriate. This guidance builds upon existing policy regarding the labeling of companion diagnostics. In its 2014 guidance, the FDA stated that if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group of therapeutic products, the companion diagnostic's intended use/indications for use should name the specific group of therapeutic products, rather than specific products. The 2020 guidance expands on the policy statement in the 2014 guidance by recommending that companion diagnostic developers consider a number of factors when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support

a broader labeling claim such as use with a specific group of oncology therapeutic products (rather than listing an individual therapeutic product(s)).

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the U.S., the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import and post-market surveillance. Unless an exemption applies, diagnostic tests require pre-notification marketing clearance or approval from the FDA prior to commercial distribution.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval (PMA) simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. For federal fiscal year 2022 the standard fee is $374,858 and the small business fee is $93,714.

Healthcare Compliance

In the U.S., biopharmaceutical manufacturers and their products are subject to extensive regulation at the federal and state level, such as laws intended to prevent fraud and abuse in the healthcare industry. Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to healthcare providers and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, including certain laws and regulations applicable only if we have marketed products, include the following:

- federal false claims, false statements, and civil monetary penalties laws prohibiting, among other things, any person from knowingly presenting, or causing to be presented, a false claim for payment of government funds or knowingly making, or causing to be made, a false statement to get a false claim paid;
- federal healthcare program anti-kickback law, which prohibits, among other things, persons from offering, soliciting, receiving, or providing remuneration, directly or indirectly, to induce either the referral of an individual for, or the purchasing or ordering of, a good or service for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which, in addition to privacy protections applicable to healthcare providers and other entities, prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs;
- federal Open Payments (or federal "sunshine" law), which requires pharmaceutical and medical device companies to monitor and report certain financial interactions with certain healthcare providers to the Center for Medicare & Medicaid Services (CMS) within the HHS for re-disclosure to the public, as well as ownership and investment interests held by certain healthcare providers and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- analogous state laws and regulations, including: state anti-kickback and false claims laws; state laws requiring pharmaceutical companies to comply with specific compliance standards, restrict financial interactions between pharmaceutical companies and healthcare providers or require pharmaceutical companies to report information related to payments to health care providers or marketing expenditures; and state laws governing privacy, security and breaches of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts; and
- laws and regulations prohibiting bribery and corruption such as the FCPA, which, among other things, prohibits U.S. companies and their employees and agents from authorizing, promising, offering, or providing, directly or indirectly, corrupt or improper payments or anything else of value to foreign government officials, employees of public international organizations or foreign government-owned or affiliated entities, candidates for foreign public office, and foreign political parties or officials thereof.

Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, exclusion from participation in federal and state health care programs, such as Medicare and Medicaid. Ensuring compliance is time consuming and costly. Similar healthcare laws and regulations exist in the European Union (EU) and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers and laws governing the privacy and security of personal information.

Coverage and Reimbursement

In the U.S. and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the U.S. such as Medicare and Medicaid, commercial health insurers, and managed care organizations, provide coverage and establish adequate reimbursement levels for the product. In the U.S., no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Additionally, companies may also need to provide discounts to purchasers, private health plans, or government healthcare programs. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, our operations, and financial condition. Factors that payors consider in determining reimbursement are based on whether the product is (i) a covered benefit under its health plan; (ii) safe, effective, and medically necessary; (iii) appropriate for the specific patient; (iv) cost-effective; and (v) neither experimental nor investigational. Additionally, a third-party payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product and the level of coverage and reimbursement can differ significantly from payor to payor.

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 U.S. 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. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price (ASP) and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs.

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

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of drug products, limiting coverage and reimbursement for medical products and other changes to the healthcare system in the U.S.

In March 2010, the U.S. Congress enacted the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the PPACA), which, among other things, includes changes to the coverage and payment for pharmaceutical products under government healthcare programs. Other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. Pursuant to the Coronavirus Aid, Relief and Economic Security Act (CARES Act) and subsequent legislation, these Medicare sequester reductions have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect, with the full 2% cut resuming thereafter.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017 (the Tax Act), which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020, and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden rescinded those orders and

issued a new executive order that directs federal agencies to reconsider rules and other policies that limit access to healthcare, and consider actions that will protect and strengthen that access. Under this order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and under the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Pharmaceutical Prices

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

In addition, in October 2020 HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program (SIP) to import certain prescription drugs from Canada into the U.S. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico, and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed by the Biden administration until January 1, 2023.

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

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, and wholesale distributors, to disclose information about pricing of

pharmaceuticals. In addition, regional healthcare organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription pharmaceutical and other healthcare programs. These measures could reduce the ultimate demand for our product candidates, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Federal and State Data Privacy Laws

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

At the state level, California has enacted data privacy and security legislation. Known as the California Consumer Privacy Act (CCPA), it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020, and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Additionally, effective starting on January 1, 2023, the California Privacy Rights Act (CPRA) will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. The CCPA and CPRA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and individually identifiable health information. These provisions may apply to some of our business activities. In addition, other states, including Virginia and Colorado, already have passed state privacy laws and other states will likely be considering similar laws in the near future.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our current or future business activities, including certain clinical research, sales and marketing practices, and the provision of certain items and services to our customers, could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that a healthcare company may fail to comply fully with one or more of these requirements. If our operations are found to be in violation of any of the privacy or data security laws or regulations described above that are applicable to us, or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal,

civil, and administrative penalties, damages, fines, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, 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. To the extent that any product candidates we may develop, once approved, are sold in a foreign country, we may be subject to similar foreign laws.

Approval and Regulation of Medical Products in the EU

In addition to regulations in the U.S., we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products outside of the U.S. Whether or not we obtain FDA approval for a product candidate, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the 27-member EU, before we may commence clinical trials or market products in those countries or areas. In the EU, our product candidates also may be subject to extensive regulatory requirements. As in the U.S., medicinal products can be marketed only if a marketing authorization from the competent regulatory agencies has been obtained. Similar to the U.S., the various phases of preclinical and clinical research in the EU are subject to significant regulatory controls.

With the exception of the EU/European Economic Area (EEA) applying the harmonized regulatory rules for medicinal products, the approval process and requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary greatly between countries and jurisdictions and can involve additional testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Clinical Trials

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on GCP, and the related national implementing provisions of the individual EU Member States govern the system for the approval of clinical trials in the EU. Under this system, a sponsor must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the sponsor may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an IMPD (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, and where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents. All suspected unexpected serious adverse reactions to the investigational drug product that occur during the clinical trial have to be reported to the competent national authority and the ethics committee of the Member State where they occurred.

In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (the Clinical Trials Regulation), was adopted. The Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The Clinical Trials Regulation entered into force on January 31, 2022, following confirmation of full functionality of the Clinical Trials Information System through an independent audit by the European Commission in mid-2020. The Clinical Trials Regulation will come into application in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC. The conduct of all clinical trials performed in the EU

will continue to be bound by currently applicable provisions until the Clinical Trials Regulation becomes applicable at the end of January 2022. According to the transitional provisions, if a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable, the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

Parties conducting certain clinical trials must, as in the U.S., post clinical trial information in the EU at the EudraCT website: https://eudract.ema.europa.eu.

Marketing Authorization in the EU

Marketing authorization applications (MAAs) can be filed either under the so-called centralized or national authorization procedures, albeit through the Mutual Recognition or Decentralized procedure for a product to be authorized in more than one EU member state.

The centralized procedure provides for the grant of a single marketing authorization following a favorable opinion by the European Medicines Agency (EMA) that is valid in all EU Member States, as well as Iceland, Liechtenstein, and Norway, which are part of the EEA. The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, advanced-therapy medicines (such as gene-therapy, somatic cell-therapy or tissue-engineered medicines), and products with a new active substance indicated for the treatment of specified diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases, and other immune dysfunctions and viral diseases. The centralized procedure is optional for products that represent a significant therapeutic, scientific, or technical innovation, or whose authorization would be in the interest of public health. Under the centralized procedure the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the sponsor in response to questions asked by the Committee for Medicinal Products for Human Use (CHMP). Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is of 150 days, excluding stop-clocks.

There are also two other possible routes to authorize medicinal products in several EU countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- *Decentralized procedure*. Using the decentralized procedure, a sponsor may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure. The sponsor may choose a member state as the reference member state to lead the scientific evaluation of the application.
- *Mutual recognition procedure*. In the mutual recognition procedure, a medicine is first authorized in one EU Member State (which acts as the reference member state), in accordance with the national procedures of that country. Following this, further marketing authorizations can be progressively sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization produced by the reference member state.

Under the above-described procedures, before granting the marketing authorization, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety, and efficacy.

Conditional Approval

In particular circumstances, EU legislation (Article 14–a Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizations for Medicinal Products for Human Use) enables sponsors to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the product candidate is intended for the treatment, prevention, or medical diagnosis of seriously debilitating or life-threatening diseases; (2) the product candidate is intended to meet unmet medical

needs of patients; (3) a marketing authorization may be granted prior to submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required; (4) the risk-benefit balance of the product candidate is positive, and (5) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

Pediatric Studies

Prior to obtaining a marketing authorization in the EU, sponsors have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan (PIP), covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are set forth in Regulation (EC) No 1901/2006, which is referred to as the Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form, or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA PDCO) may grant deferrals for some medicines, allowing a company to delay development of the medicine in children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine in children is not needed or is not appropriate because (a) the product is likely to be ineffective or unsafe in part or all of the pediatric population; (b) the disease or condition occurs only in adult population; or (c) the product does not represent a significant therapeutic benefit over existing treatments for pediatric population. Before a marketing authorization application can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

PRIME Designation

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

Periods of Authorization and Renewals

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

the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause).

Regulatory Requirements after Marketing Authorization

As in the U.S., both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. The holder of an EU marketing authorization for a medicinal product must, for example, comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. The manufacturing process for medicinal products in the EU is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, including compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the EU, the advertising and promotion of approved products are subject to EU Member States' laws governing promotion of medicinal products, interactions with clinicians, misleading and comparative advertising, and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics (SmPC) as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion, which is prohibited in the EU.

Regulatory Exclusivity

In the EU, new products authorized for marketing (*i.e.,* reference products) qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic sponsors from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic marketing authorization in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic sponsor from commercializing its product in the EU until ten years have elapsed from the initial authorization of the reference product in the EU. The ten-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Orphan Drug Designation and Exclusivity

The criteria for designating an orphan medicinal product in the EU are similar in principle to those in the U.S. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention, or treatment of a life- threatening or chronically debilitating condition, (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment, and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition. The term 'significant benefit' is defined in Regulation (EC) 847/2000 to mean a clinically relevant advantage or a major contribution to patient care.

Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. During this ten year market exclusivity period, the EMA or the competent authorities of the Member States of the EEA, cannot accept an application for a marketing authorization for a similar medicinal product for the same indication. A similar medicinal product is defined as a medicinal product containing a similar active

substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The application for orphan designation must be submitted before the application for marketing authorization. The sponsor will receive a fee reduction for the MAA if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The ten-year market exclusivity in the EU may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if: (1) the second sponsor can establish that its product, although similar, is safer, more effective, or otherwise clinically superior; (2) the sponsor consents to a second orphan medicinal product application; or (3) the sponsor cannot supply enough orphan medicinal product.

Pediatric Exclusivity

If a sponsor obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate (SPC) or alternatively a one year extension of the regulatory market exclusivity from ten to eleven years, as selected by the marketing authorization holder.

Patent Term Extensions

The EU also provides for patent term extension through SPCs. The rules and requirements for obtaining a SPC are similar to those in the U.S. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained. Although SPCs are available throughout the EU, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the EU.

Reimbursement and Pricing of Prescription Pharmaceuticals

In the EU, similar political, economic, and regulatory developments to those in the U.S. may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the U.S. and the EU, reimbursement and healthcare payment systems vary significantly by country and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, pharmaceutical firms may be required to conduct a clinical trial that compares the cost-effectiveness of the product to other available therapies.

The EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU Member States may approve a specific price for a product, or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other Member States allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on healthcare costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained.

Reference pricing used by various EU Member States, and parallel trade (*i.e.*, 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 product candidates, if approved in those countries.

Approval of Companion Diagnostic Devices

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

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

General Data Protection Regulation

Many countries outside of the U.S. maintain rigorous laws governing the privacy and security of personal information. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the EEA, and the processing of personal data that takes place in the EEA, is subject to the General Data Privacy Regulation (GDPR), which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, and it imposes heightened requirements on companies that process health and other sensitive data, such as requiring in many situations that a company obtain the consent of the individuals to whom the sensitive personal data relate before processing such data. Examples of obligations imposed by the GDPR on companies processing personal data that fall within the scope of the GDPR include providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, appointing a data protection officer, providing notification of data breaches, and taking certain measures when engaging third-party processors.

The GDPR also imposes strict rules on the transfer of personal data to countries outside the EEA, including the U.S., and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR is a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. In July 2020 the Court of Justice of the European Union (CJEU) invalidated the EU-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual

clauses, for transfers of personal data from the EEA to the U.S. Following the withdrawal of the United Kingdom (U.K.) from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR.

Brexit and the Regulatory Framework in the United Kingdom

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

Other U.S. environmental, health, and safety laws and regulations

We may be subject to numerous environmental, health, and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment, and disposal of hazardous materials and wastes. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us. In addition, we may incur substantial costs in order to comply with current or future environmental, health, and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development, or production efforts. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties, or other sanctions.

Employees and Human Capital

As of December 31, 2021, we had 40 full-time employees, of which 29 are engaged in research and development. 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.

We consider the intellectual capital of our employees to be an essential driver of our business. Our workforce expanded during fiscal 2021; new employees were hired to support our clinical and preclinical pipeline, with additions in our research, clinical development, operations and general and administrative functions. We expect to continue to add additional employees in 2022 with a focus on increasing expertise in clinical and preclinical research and development.

We continually evaluate our business needs and opportunities and strive to balance in house expertise and capacity with outsourced expertise and capacity. Currently, we outsource substantially all clinical trial work to clinical research organizations and drug substance and finished drug product manufacturing to contract manufacturers.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees and consultants through the granting of stock-based compensation awards and to align such awards with the interests of our stockholders. We provide a comprehensive benefits package to help employees manage health, well-being, finances and life outside of work, including health insurance, dental and vision insurance, life insurance, short-term and long-term disability insurance, paid sick leave, a 401(k) plan, a flexible spending account program and paid vacation time.

We value the health, safety and wellbeing of our employees and their families. In response to the COVID-19 pandemic, we implemented safety measures that we determined were in the best interest of our employees, along with measures designed to protect the health of all those entering our office.

Information about our Executive Officers (as of March 15, 2022)

Name	Age	Position
James R. Porter, Ph.D.	46	Chief Executive Officer, President and Director
Alexandra Balcom	38	Chief Financial Officer and Treasurer
Deborah Miller, Ph.D., J.D.	46	Chief Legal Officer and Secretary
Darlene Noci	45	SVP of Product Development & Regulatory Affairs
Christopher D. Turner, M.D.	54	Chief Medical Officer

James R. Porter, Ph.D., has served as our Chief Executive Officer and President and as a member of our board of directors since February 2020. Prior to that, Dr. Porter served as our Vice President, Product Development from April 2018 to January 2020 and worked as a consultant to the Company from January 2018 to April 2018. From July 2002 to December 2016, Dr. Porter held various roles at Infinity, including most recently as Vice President of Product Development. Over the course of over 14 years at Infinity, he contributed to the research and development programs of six different compounds entering clinical trials. As the duvelisib product development team leader, Dr. Porter led a cross-functional development team from development candidate nomination through NDA submission, resulting in the FDA approval of COPIKTRA® for patients with follicular lymphoma, small lymphocytic lymphoma, and chronic lymphocytic leukemia. Following Infinity's licensing of duvelisib to Verastem, Inc., a biopharmaceutical company (Verastem), Dr. Porter served as Consultant, Product Development at Verastem from January 2017 to December 2017, where he led the transition, product development team, and NDA submission for the duvelisib program. Dr. Porter received his B.A. in chemistry at the College of the Holy Cross and his Ph.D. in organic chemistry from Boston College.

Alexandra Balcom, MBA, CPA, has served as our Chief Financial Officer since January 2021. Ms. Balcom brings over 15 years of strategic, financial and operational experience in the biotechnology industry to her role. Before joining Nuvalent, she held various roles at SQZ Biotechnologies Company, a biotechnology company, from April 2017 to March 2021, including Vice President of Finance, where she was responsible for strategic planning, finance and accounting. Prior to that, Ms. Balcom served as Corporate Controller at Agios Pharmaceuticals Inc., a pharmaceutical company. Ms. Balcom was responsible for all financial functions of the company including strategic planning, treasury, tax, finance, and accounting. Earlier in her career, Ms. Balcom held positions at both Molecular Insight Pharmaceuticals Inc., a pharmaceutical company that was acquired by Progenics Pharmaceuticals, Inc., a biotechnology company, in 2013 and Coley Pharmaceutical Group, Inc., a biopharmaceutical company that was acquired by Pfizer in 2007. Ms. Balcom earned her B.B.A. in finance from the University of Massachusetts, Amherst and her M.B.A. from Boston College. Ms. Balcom is also a certified public accountant in Massachusetts.

Deborah Miller, Ph.D., J.D., has served as our Chief Legal Officer since June 2021. Before joining Nuvalent, she held various roles at Sumitomo Dainippon Pharma America, Inc., a pharmaceutical company (SDPA), from April 2020 to June 2021, including Senior Vice President, Deputy General Counsel and Chief IP Counsel, where she was responsible for providing legal services to all of the North American companies of Sumitomo Dainippon Pharma Co., Ltd. (Sumitomo). Prior to that, Dr. Miller served as Deputy General Counsel & Chief IP Counsel at Sunovion Pharmaceuticals Inc., a subsidiary of SDPA, from March 2017 to April 2020 and held various roles at Infinity from March 2010 to March 2017, including Vice President, Deputy General Counsel and Chief Patent

Counsel, where she built and managed the intellectual property group and supported various in-licensing, out-licensing and financing ventures. Earlier in her career, Dr. Miller was IP corporate counsel at Sepracor Inc. (currently, Sunovion Pharmaceuticals Inc.), a biopharmaceutical company, which was acquired by Sumitomo in 2010, and an associate at the law firm Nutter McClennen & Fish LLP. She received her B.A. in chemistry from Swarthmore College, her M.M.Sc. from Harvard Medical School, her Ph.D. in biological chemistry and molecular pharmacology from Harvard University and her J.D. from Suffolk University Law School.

Darlene Noci, A.L.M., has served as our Senior Vice President of Product Development & Regulatory Affairs since January 2021. Before joining Nuvalent, she founded her own regulatory consulting firm, Noci Strategic Consulting, LLC, in May 2018. Prior to that, Ms. Noci served as Vice President, Regulatory Affairs and Quality Assurance at X4 Pharmaceuticals, Inc., a biopharmaceutical company, from January 2016 to May 2018. Prior to that, Ms. Noci served as Global Regulatory Lead Strategist, Immuno-Oncology at EMD Serono, the North America biopharma business of Merck KgaA, Darmstadt, Germany, a pharmaceutical company, from June 2014 to January 2016, where she led the global regulatory strategy and portfolio for Bavencio®, the company's anti-programmed death-ligand 1 antibody. Prior to that, she held various roles at several biotechnology companies, including Infinity, Sanofi and Genzyme (acquired by Sanofi in 2011). Ms. Noci received her B.A. from Adelphi University and her A.L.M. in government from Harvard University Extension School.

Christopher D. Turner, M.D., has served as our Chief Medical Officer since March 2021. Before joining Nuvalent, Dr. Turner served as Vice President of Clinical Development at Blueprint Medicines Corporation, a global precision therapy company, from June 2018 to March 2021, where he oversaw the development and approval of kinase inhibitor GAVRETO™ (pralsetinib) in RET-fusion positive NSCLC and RET-altered thyroid cancer. From July 2014 to May 2018, Dr. Turner served as Vice President of Clinical Science at Celldex Therapeutics, Inc., a biopharmaceutical company, where he led the development of novel antibody-drug conjugate and immune-oncology pipeline compounds. From July 2008 to July 2014, Dr. Turner held various roles at ARIAD Pharmaceuticals, Inc., a pharmaceutical company that was acquired by Takeda Oncology in 2017, including Head of Clinical Research, where he led the development of ICLUSIG® (ponatinib), a kinase inhibitor therapy for patients with chronic myeloid leukemia, and ALUNBRIG® (brigatinib), a kinase inhibitor therapy for patients with ALK positive NSCLC. Prior to that, Dr. Turner was Director of the Pediatric Neuro-Oncology Outcomes Clinic at the Dana-Farber Cancer Institute/Children's Hospital Boston and an Instructor of Pediatrics at Harvard Medical School. Dr. Turner is board certified in both Pediatrics and Pediatric Hematology and Oncology and is a Fellow of the American Academy of Pediatrics. He received his B.A. in biochemistry from Bowdoin College and his M.D. from the University of Rochester School of Medicine and Dentistry. He completed a residency in General Pediatrics at Children's National Medical Center in Washington, DC and fellowships in both Pediatric Hematology/Oncology and Pediatric Neuro-Oncology at Duke University Medical Center in Durham, North Carolina.

Our Corporate Information

We were incorporated under the laws of the state of Delaware on January 25, 2017 under the name Nuvalent, Inc.

Our principal executive offices are located at One Broadway, 14th Floor, Cambridge, MA 02142 and our telephone number is (857) 357-7000. Our website address is http://www.nuvalent.com. The information contained on, or accessible through, our website does not constitute part of this Annual Report. We have included our website address in this Annual Report solely as an inactive textual reference.

Available Information

Our Internet address is *www.nuvalent.com*. Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act are available through the "Investors" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or SEC. Information on our website is not part of this Annual Report or any of our other securities filings unless specifically incorporated herein by reference. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at *http://www.sec.gov*. All statements made in any of our securities filings,

including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

ITEM 1A. RISK FACTORS

Risk Factors

Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report and in other documents that we file with the Securities and Exchange Commission, or SEC, in evaluating the Company and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occur, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impact our business, prospects, financial condition and results of operations.

Item 1A. Risk Factors.

In evaluating the Company and our business, careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report and in other documents that we file with the SEC. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties were to actually occur, our business, prospects, financial condition or results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition or results of operations.

Risks related to our financial position and need for additional capital

We are very early in our development efforts, have a limited operating history, have not completed any clinical trials, have no products approved for commercial sale and have not generated any revenue, which may make it difficult for investors to evaluate our current business and likelihood of success and viability.

We are a biopharmaceutical company with a limited operating history upon which investors can evaluate our business and prospects. We were incorporated in January 2017 and commenced significant operations in 2018, have never completed any clinical trials, have no products approved for commercial sale and have never generated any revenue. Drug development is a highly uncertain undertaking and involves a substantial degree of risk. To date, we have devoted substantially all of our resources to research and development activities, including with respect to NVL-520, our ROS1-selective inhibitor, and NVL-655, our ALK-selective inhibitor, and our ALK IXDN, HER2 and other discovery programs, business planning, establishing and maintaining our intellectual property portfolio, hiring personnel, raising capital and providing general and administrative support for these operations.

We have not yet demonstrated our ability to successfully complete any clinical trials, obtain marketing approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. As a result, it may be more difficult for investors to accurately predict our likelihood of success and viability than it could be if we had a longer operating history.

In addition, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and risks frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields. We also expect that, as we advance our product candidates, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We have not yet demonstrated an ability to successfully overcome such risks and difficulties, or to make such a transition. If we do not adequately address these risks and difficulties or successfully make such a transition, our business will suffer.

We have incurred significant net losses in each period since our inception, and we expect to continue to incur significant net losses for the foreseeable future.

We have incurred significant net losses in each reporting period since our inception, have not generated any revenue to date and have financed our operations principally through private placements of our Series A and Series B convertible preferred stock, the issuance of convertible notes (which converted to convertible preferred stock in 2018), debt financing from stockholders (which was settled in convertible preferred stock in February 2021), and most recently, with proceeds from the sale of common stock in the IPO completed in August 2021. Our net losses were $46.3 million and $14.6 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $78.2 million. We are still in the early stages of development of our product candidates and have not yet completed any clinical trials. As a result, we expect that it will be several years, if ever, before we have a commercialized product and generate revenue from product sales. Even if we succeed in receiving marketing approval for and commercializing one or more of our product candidates, we expect that we will continue to incur substantial research and development and other expenses in order to discover, develop and market additional potential products.

We expect to continue to incur significant and increasing expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. The size of our future net losses will depend, in part, on the pace of our development activities and the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our working capital, our ability to fund the development of our product candidates and our ability to achieve and maintain profitability and the performance of our stock.

Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve our objectives relating to the discovery, development and commercialization of our product candidates.

We rely on our team's expertise in chemistry, structure-based drug design, oncology drug development, business development and our patient-driven approach to develop our product candidates. Our business depends significantly on the success of our approach and the development and commercialization of the product candidates that we discover with this approach. We have no products approved for commercial sale and do not anticipate generating any revenue from product sales for the next several years, if ever. Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve several objectives, including:

- successful and timely completion of preclinical and clinical development of NVL-520, NVL-655 and any future product candidates from our ALK IXDN, HER2 and other discovery programs, and any other future programs;
- establishing and maintaining relationships with CROs and clinical sites for the clinical development of NVL-520, NVL-655 and any future product candidates from our ALK IXDN, HER2 and other current or future discovery programs;
- timely receipt of marketing approvals from applicable regulatory authorities for any product candidates for which we successfully complete clinical development;
- developing an efficient and scalable manufacturing process for our product candidates, including the production of finished products that are appropriately packaged for sale if our product candidates obtain marketing approvals;
- establishing and maintaining commercially viable supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and meet the market demand for our product candidates, if approved;
- successful commercial launch following any marketing approval, including the development of a commercial infrastructure, whether in-house or with one or more collaborators;
- a continued acceptable safety profile following any marketing approval of our product candidates;

- commercial acceptance of our product candidates by patients, the medical community and third-party payors, including the willingness of physicians to use our product candidates, if approved, in lieu of (or as a second-line treatment in conjunction with) other approved therapies;
- satisfying any required post-marketing approval commitments to applicable regulatory authorities;
- identifying, assessing and developing new product candidates;
- obtaining, maintaining and expanding patent protection, trade secret protection and regulatory exclusivity, both in the U.S. and internationally;
- defending against third-party interference or infringement claims, if any;
- entering into, on favorable terms, any collaboration, licensing or other arrangements that may be necessary or desirable to develop, manufacture or commercialize our product candidates;
- obtaining coverage and adequate reimbursement by third-party payors for our product candidates, if approved;
- addressing any competing therapies and technological and market developments; and
- attracting, hiring and retaining qualified personnel.

We may never be successful in achieving our objectives and, even if we do, may never generate revenue that is significant or large enough to achieve profitability. 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 decrease the value of our company and could impair our ability to maintain or further our research and development efforts, raise additional necessary capital, grow our business and continue our operations.

We will require substantial additional capital to finance our operations. If we are unable to raise such capital when needed, or on acceptable terms, we may be forced to delay, reduce or eliminate one or more of our research and drug development programs, future commercialization efforts, product development or other operations.

Since our inception, we have used substantial amounts of cash to fund our operations, and our expenses will increase substantially in the foreseeable future in connection with our ongoing activities, particularly as we continue the research and development of, initiate clinical trials of, and seek marketing approval for, our product candidates. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. Even if one or more of our product candidates or any future product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with sales, marketing, manufacturing and distribution activities. Our expenses could increase beyond expectations if we are required by the FDA, the EMA or other regulatory authorities to perform clinical trials or preclinical studies in addition to those that we currently anticipate. Other unanticipated costs may also arise. Because the design and outcome of our clinical trials, including our planned and anticipated clinical trials, are highly uncertain, we cannot reasonably estimate the actual amount of resources and funding that will be necessary to successfully complete the development and commercialization of our product candidates or any future product candidates that we develop. The FDA has confirmed clinical investigation of NVL-520 and NVL-655 may proceed. We recently initiated a Phase 1/2 clinical trial for NVL-520, and plan to initiate a Phase 1/2 clinical trial for NVL-655 in the second quarter of 2022. We have not yet received clearance to begin clinical trials for any of our other product candidates, and we are not permitted to market or promote any product candidate before we receive marketing approval from the FDA, EMA or any comparable foreign regulatory authorities. We are also incurring additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in order to continue our operations.

Based on our current operating plan, we believe that our existing cash, cash equivalents and marketable securities as of the date of this Annual Report, will be sufficient to fund our operating expenses and capital expenditure requirements into 2024. Advancing the development of NVL-520, NVL-655 and our ALK IXDN, HER2 and other discovery programs will require a significant amount of capital. Our existing cash, cash equivalents and marketable securities will not be sufficient to fund any of our product candidates through regulatory approval,

and we anticipate needing to raise additional capital to complete the development and commercialization of our product candidates. Our estimate as to how long we expect our existing cash, cash equivalents and marketable securities to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned.

We will be required to obtain further funding through public or private equity financings, debt financings, collaborative agreements, licensing arrangements or other sources of financing, which may dilute our stockholders or restrict our operating activities. We do not have any committed external source of funds. Adequate additional financing may not be available to us on acceptable terms, or at all. To the extent that we raise additional capital through the sale of equity or convertible debt securities, each investor's ownership interests will be diluted, and the terms may include liquidation or other preferences that adversely affect each investor's rights as a stockholder. Debt financing may result in imposition of debt covenants, increased fixed payment obligations or other restrictions that may affect our business. If we raise additional funds through upfront payments or milestone payments pursuant to strategic collaborations with third parties, we may have to relinquish valuable rights to our product candidates or grant licenses on terms that are not favorable to us. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

Our failure to raise capital as and when needed or on acceptable terms would have a negative impact on our financial condition and our ability to pursue our business strategy, and we may have to delay, reduce the scope of, suspend or eliminate one or more of our research or drug development programs, clinical trials or future commercialization efforts.

Risks related to the discovery, development and commercialization of our product candidates

We are very early in our development efforts and our future prospects are substantially dependent on NVL-520 and NVL-655. If we are unable to advance these product candidates through development, obtain regulatory approval and ultimately commercialize such product candidates, or experience significant delays in doing so, our business will be materially harmed.

We are very early in our development efforts. We recently initiated a Phase 1/2 clinical trial for NVL-520, and plan to initiate a Phase 1/2 clinical trial for NVL-655 in the second quarter of 2022. All of our other product candidates are still in preclinical development and have never been tested in humans. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful preclinical and clinical development and eventual commercialization of one or more product candidates. We are not permitted to market or promote any product candidate before we receive marketing approval from the FDA, EMA or any comparable foreign regulatory authorities, and we may never receive such marketing approvals.

The success of NVL-520 and NVL-655 will depend on several factors, including the following:

- successful and timely completion of preclinical studies;
- submission of INDs in the U.S. and CTAs and/or comparable applications outside the U.S. for regulatory authority review and agreement to proceed with our clinical trials;
- our ability to address any potential delays resulting from factors related to the COVID-19 pandemic;
- successful initiation and completion of clinical trials;
- successful and timely patient selection and enrollment in and completion of clinical trials;
- maintaining and establishing relationships with CROs and clinical sites for the clinical development of our product candidates both in the U.S. and internationally;
- maintaining and growing an organization of chemists, medical professionals and clinical development professionals who can develop and commercialize our product candidates;

- the frequency and severity of adverse events in clinical trials;
- obtaining positive data that support demonstration of efficacy, safety and tolerability profiles and durability of effect for our product candidates that are satisfactory to the FDA, EMA or any comparable foreign regulatory authority for marketing approval;
- the timely receipt of marketing approvals from applicable regulatory authorities;
- the timely identification, development and approval of companion diagnostic tests, if required;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- the maintenance of existing or the establishment of new supply arrangements with third-party drug product suppliers and manufacturers for clinical development and, if approved, commercialization of our product candidates;
- obtaining and maintaining patent protection, trade secret protection and regulatory exclusivity, both in the U.S. and internationally;
- the protection of our rights in our intellectual property portfolio;
- establishing sales, marketing and distribution capabilities and the successful launch of commercial sales of our product candidates if and when approved for marketing, whether alone or in collaboration with others;
- a continued acceptable safety profile following any marketing approval;
- commercial acceptance by patients, the medical community and third-party payors, including the willingness of physicians to use our product candidates, if approved, in lieu of (or as a second-line treatment in conjunction with) other approved therapies; and
- our ability to compete with other therapies.

We do not have complete control over many of these factors, including certain aspects of preclinical and clinical development and the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any future collaborator. If we are not successful with respect to one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize any product candidates from our lead programs, which would materially harm our business. If we do not receive marketing approvals for such product candidates, we may not be able to continue our operations.

Our preclinical studies and clinical trials may fail to adequately demonstrate the safety and efficacy of any of our product candidates, which would prevent or delay development, regulatory approval and commercialization.

Before obtaining marketing approval from the FDA, EMA or other comparable foreign regulatory authorities for the sale of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical studies and clinical trials that our product candidates are both safe and effective for use in each target indication. Preclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and the ultimate outcome is uncertain. Failure can occur at any time during the preclinical study and clinical trial processes, and, because our product candidates are in an early stage of development, there is a high risk of failure, and we may never succeed in developing marketable products.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent receipt of marketing approval or our ability to commercialize our product candidates, including:

- failure of our product candidates in preclinical studies or clinical trials to demonstrate safety and efficacy;
- receipt of feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- negative or inconclusive clinical trial results that may require us to conduct additional clinical trials or abandon certain research, discovery and/or drug development programs;

- the number of patients required for clinical trials being larger than anticipated, enrollment in these clinical trials being slower than anticipated, particularly if there are other trials enrolling the same or overlapping precisely targeted patient populations, or participants dropping out of these clinical trials at a higher rate than anticipated;
- third-party contractors failing to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- the suspension or termination of our clinical trials for various reasons, including non-compliance with regulatory requirements or a finding that our product candidates have undesirable adverse events or other unexpected characteristics or risks;
- the cost of clinical trials of our product candidates being greater than anticipated;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates being insufficient or inadequate; and
- regulators revising the requirements for approving our product candidates.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we are currently contemplating, if we are unable to successfully complete clinical trials of our product candidates or other testing in a timely manner, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may incur unplanned costs, be delayed in seeking and obtaining marketing approval, if we receive such approval at all, receive more limited or restrictive marketing approval, be subject to additional post-marketing testing requirements or have the drug removed from the market after obtaining marketing approval.

Our discovery and preclinical development activities are focused on the development of targeted therapeutics for patients with cancer-associated genomic alterations, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs may never lead to approved or marketable products.

The discovery and development of targeted therapeutics for patients with cancer-associated genomic alterations is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are evolving. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. Although we believe, based on our preclinical work, that the genomic alterations targeted by our programs are oncogenic drivers, clinical results may not confirm this hypothesis or may only confirm it for certain alterations or certain tumor types. The patient populations for our product candidates are limited to those with specific target alterations and may not be completely defined but are substantially smaller than the general treated cancer population, and we will need to screen and identify these patients with targeted alterations. Successful identification of patients is dependent on several factors, including achieving certainty as to how specific alterations respond to our product candidates and the ability to identify such alterations, which may require the use of companion diagnostic tests. Furthermore, even if we are successful in identifying patients, we cannot be certain that the resulting patient populations for each mutation will be large enough to allow us to successfully obtain approval for each mutation type and commercialize our product candidates and achieve profitability. We do not know if our approach of focusing on treating patients with cancer-associated genomic alterations will be successful, and if our approach is unsuccessful, our business will suffer.

Any delays in the commencement or completion, or termination or suspension, of our planned or future clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Before we can initiate clinical trials of a product candidate in any indication, we must submit the results of preclinical studies to the FDA, EMA or other comparable foreign regulatory authorities 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 similar regulatory submission under which we must receive authorization to proceed with clinical development. The FDA, EMA or other comparable foreign regulatory

authorities may require us to conduct additional preclinical studies for any product candidate before they allow us to initiate clinical trials under any IND, CTA or comparable application which may lead to additional delays and increase the costs of our preclinical development programs.

Before obtaining marketing approval from the FDA of NVL-520 or NVL-655 or of any other future product candidate in any indication, we must conduct extensive clinical studies to demonstrate safety and efficacy. Clinical testing is expensive, time consuming and uncertain as to outcome. In addition, we expect to rely in part on preclinical, clinical and quality data generated by our CROs and other third parties for regulatory submissions for our product candidates. While we have or will have agreements governing these third parties' services, we have limited influence over their actual performance. If these third parties do not make data available to us, or, if applicable, make regulatory submissions in a timely manner, in each case pursuant to our agreements with them, our development programs may be significantly delayed and we may need to conduct additional studies or collect additional data independently. In either case, our development costs would increase. We recently initiated a Phase 1/2 clinical trial for NVL-520, and plan to initiate a Phase 1/2 clinical trial for NVL-655 in the second quarter of 2022. IND submission must become effective prior to initiating any clinical trials in the U.S. for any of our future product candidates.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRB or IEC of the institutions in which such trials are being conducted, by a DSMB for such trial or by the FDA or foreign regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse events, failure to demonstrate a benefit from using a pharmaceutical, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, changes in regulatory requirements and policies may occur, and we may need to amend clinical trial protocols to comply with these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs/ECs for reexamination, which may impact the costs, timing or successful completion of a clinical trial.

Certain of our current or future scientific advisors or consultants who receive compensation from us may become investigators for our future clinical trials. Under certain circumstances, we may be required to report some of these relationships to the FDA. Although we expect any such relationships to be within the FDA's guidelines, the FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of our product candidates. If we experience delays in the completion of, or termination of, any clinical trial of any product candidate, the commercial prospects of such product candidate will be harmed, and our ability to generate product revenues will be delayed. Moreover, any delays in completing our clinical trials will increase our costs, slow down our development and approval process and jeopardize our ability to commence product sales and generate revenues, which may harm our business, financial condition, results of operations and prospects significantly.

The outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials, and the results of our clinical trials may not satisfy the requirements of the FDA, EMA or other comparable foreign regulatory authorities.

We will be required to demonstrate with substantial evidence through well-controlled clinical trials that our product candidates are safe and effective for use in a diverse population before we can seek marketing approvals for their commercial sale. Preclinical and clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the preclinical study and clinical trial processes, and, because our product candidates are in an early stage of development, there is a high risk of failure and we may never succeed in developing marketable products.

The results of preclinical studies may not be predictive of the results of clinical trials of our product candidates, and the results of early clinical trials may not be predictive of the results of later-stage clinical trials. Although product candidates may demonstrate promising results in preclinical studies and early clinical trials, they may not prove to be safe or effective in subsequent clinical trials. Favorable results from certain animal studies may not accurately predict the results of other animal studies or of human trials, due to the inherent biologic differences in species, the differences between testing conditions in animal studies and human trials, and the particular goals, purposes, and designs of the relevant studies and trials. We have, for example, observed preclinical CNS activity of NVL-520 and NVL-655 in studies with rats and mice. These studies may or may not be predictive of CNS penetrance and activity of NVL-520 or NVL-655 in human trials. Similarly, certain of our hypotheses regarding the potential clinical and therapeutic benefits of NVL-520 and NVL-655 compared to other products or molecules in development are based on observations from our preclinical studies, and results from such preclinical studies are not necessarily predictive of the results of later preclinical studies or clinical trials.

There is typically an extremely high rate of attrition from the failure of product candidates proceeding through preclinical studies and clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. Likewise, early, smaller-scale clinical trials may not be predictive of eventual safety or effectiveness in large-scale pivotal clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their drugs. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy, insufficient durability of efficacy or unacceptable safety issues, notwithstanding promising results in earlier trials. Most product candidates that commence preclinical studies and clinical trials are never approved as products. The development of our product candidates and our stock price may also be impacted by inferences, whether correct or not, that are drawn between the success or failure of preclinical studies or clinical trials of our competitors or other companies in the biopharmaceutical industry, in addition to our own preclinical studies and clinical trials.

In some instances, there can be significant variability in safety and efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, differences in and adherence to the dose and dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. Patients treated with our product candidates may also be undergoing surgical, radiation and chemotherapy treatments and may be using other approved products or investigational new drugs, which can cause adverse events that are unrelated to our product candidates. As a result, assessments of efficacy can vary widely for a particular patient, and from patient to patient and site to site within a clinical trial. This subjectivity can increase the uncertainty of, and adversely impact, our clinical trial outcomes.

Any preclinical studies or clinical trials that we conduct may not demonstrate the safety and efficacy necessary to obtain regulatory approval to market our product candidates. If the results of our ongoing or future preclinical studies and clinical trials are inconclusive with respect to the safety and efficacy of our product candidates, if we do not meet the clinical endpoints with statistical and clinically meaningful significance, or if there are safety concerns associated with our product candidates, we may be prevented or delayed in obtaining marketing approval for such product candidates.

We do not know whether any clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain approval to market any of our product candidates.

In addition to NVL-520 and NVL-655, our prospects depend in part upon discovering, developing and commercializing additional product candidates from our ALK IXDN, HER2 and other discovery programs, which may fail in development or suffer delays that adversely affect their commercial viability.

Our future operating results are dependent on our ability to successfully discover, develop, obtain regulatory approval for and commercialize NVL-520, NVL-655 and future product candidates from our ALK IXDN, HER2 and other discovery programs. A research candidate can unexpectedly fail at any stage of development. The

historical failure rate for research candidates is high due to risks relating to safety, efficacy, clinical execution, changing standards of medical care and other unpredictable variables. The results from preclinical testing or early clinical trials of a product candidate may not be predictive of the results that will be obtained in later stage clinical trials of the product candidate.

The success of other research candidates we may develop will depend on many factors, including the following:

- generating sufficient data to support the initiation or continuation of preclinical studies and clinical trials;
- addressing any delays resulting from factors related to the ongoing COVID-19 pandemic;
- obtaining regulatory permission to initiate clinical trials;
- contracting with the necessary parties to conduct clinical trials;
- successful enrollment of patients in, and the completion of, clinical trials on a timely basis;
- the timely manufacture of sufficient quantities of a product candidate for use in clinical trials; and
- adverse events in clinical trials.

Even if we successfully advance any research candidates into preclinical and clinical development, their success will be subject to all of the preclinical, clinical, regulatory and commercial risks described elsewhere in this "Risk Factors" section. Accordingly, there can be no assurance that we will ever be able to discover, develop, obtain regulatory approval of, commercialize or generate significant revenue from any product candidates.

Our approach to the discovery and development of product candidates is unproven, and we may not be successful in our efforts to use and expand our approach to build a pipeline of product candidates with commercial value.

A key element of our strategy, which is unproven, is to use and expand our expertise in chemistry, structure-based drug design and patient-driven approach to build a pipeline of product candidates and progress these product candidates through clinical development. Although our research and development efforts to date have resulted in the discovery and clinical development of NVL-520 and preclinical development of NVL-655, such product candidates, and any other product candidates we may develop may not be safe or effective as cancer therapeutics, and we may not be able to develop any other product candidates. For example, we may not be successful in identifying genomic alterations that are oncogenic and are targeted for patient populations that result in sufficient enrollment size or present attractive commercial opportunities. Our approach is evolving and may not reach a state at which building a pipeline of product candidates is possible. Even if we are successful in building a pipeline of product candidates, the potential product candidates that we identify may not be suitable for clinical development or generate acceptable clinical data, including as a result of being shown to have unacceptable toxicity or other characteristics that indicate that they are unlikely to be product candidates that will receive marketing approval from the FDA, EMA or other regulatory authorities or achieve market acceptance. If we do not successfully develop and commercialize product candidates, we will not be able to generate product revenue in the future, which likely would result in significant harm to our financial position and adversely affect our business.

The regulatory approval processes of the FDA, EMA and other comparable foreign regulatory authorities are lengthy, time consuming and inherently unpredictable. If we are ultimately unable to obtain regulatory approval of our product candidates, we will be unable to generate product revenue and our business will be substantially harmed.

Obtaining approval by the FDA, EMA and other comparable foreign regulatory authorities is unpredictable, typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the type, complexity and novelty of the product candidates involved. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions, which may cause delays in the approval or the decision not to approve an application. Regulatory authorities have substantial discretion in the

approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other data. Even if we eventually complete clinical testing and receive approval for our product candidates, the FDA, EMA and other comparable foreign regulatory authorities may approve our product candidates for a more limited indication or a narrower patient population than we originally requested or may impose other prescribing limitations or warnings that limit the product candidate's commercial potential. Even if approved, we may be required to conduct additional studies to verify or confirm the clinical benefits of our products. We have not submitted for, or obtained, regulatory approval for any product candidate, and it is possible that none of our product candidates will ever obtain regulatory approval. Further, development of our product candidates and/or regulatory approval may be delayed for reasons beyond our control.

Applications for our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other comparable foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials;
- the FDA, EMA or other comparable foreign regulatory authorities may determine that our product candidates are not safe and effective, are only moderately effective or have undesirable or unintended adverse events, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- the FDA, EMA or other comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the clinical data of the clinical trial may fail to meet the level of statistical significance required to obtain approval of our product candidates by the FDA, EMA or other comparable foreign regulatory authorities;
- we may be unable to demonstrate to the FDA, EMA or other comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
- the FDA, EMA or other comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;
- the FDA, EMA or other comparable regulatory authorities may fail to approve companion diagnostic tests required for our product candidates;
- we may not obtain or maintain adequate funding to complete the clinical trial in a manner that is satisfactory to the FDA, EMA or other comparable foreign regulatory authorities; and
- the approval policies or regulations of the FDA, EMA or other comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process, as well as the unpredictability of the results of clinical trials, may result in our failing to obtain regulatory approval to market any of our product candidates, which would significantly harm our business, results of operations and prospects.

We have only limited experience as a company in the conduct of clinical trials.

We have only limited experience as a company in the conduct of clinical trials. In part because of this lack of experience as a company and our limited infrastructure, we cannot be certain that our preclinical studies and clinical trials will begin or be completed on time, if at all. Large-scale clinical trials would require significant additional financial and management resources and reliance on third-party clinical investigators, CROs, and consultants. Relying on third-party clinical investigators, CROs and consultants may force us to encounter delays that are outside of our control. We may be unable to identify and contract with sufficient investigators, CROs and

consultants on a timely basis or at all. There can be no assurance that we will be able to negotiate and enter into any necessary services agreement with CROs on terms that are acceptable to us on a timely basis or at all.

We may not be able to submit INDs, CTAs or comparable applications to commence clinical trials on the timelines we expect, and even if we are able to, the FDA, EMA or any comparable foreign regulatory authority may not permit us to proceed.

We have submitted INDs for NVL-520 and NVL-655 to the FDA, and the FDA has confirmed that clinical investigation of both may proceed. We recently initiated a Phase 1/2 clinical trial for NVL-520 and plan to initiate a Phase 1/2 clinical trial for NVL-655 in the second quarter of 2022. However, we may not be able to submit such IND or INDs for future product candidates on the timelines we expect or such submissions may not take effect on the timeline that we anticipate or at all. For example, we may experience manufacturing delays or other delays with IND-enabling studies. Moreover, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate clinical trials. Additionally, even if the FDA agrees with the design and implementation of the clinical trials set forth in an IND, we cannot guarantee that it will not change its requirements in the future. These considerations also apply to new clinical trials we may submit as amendments to existing INDs or to a new IND. Any failure to submit INDs, CTAs or comparable applications on the timelines we expect or to obtain regulatory approvals for our planned clinical trials may prevent us from initiating or completing our clinical trials or commercializing our product candidates on a timely basis, if at all.

Our product candidates may cause significant adverse events, toxicities or other undesirable adverse events when used alone or in combination with other approved products or investigational new drugs that may result in a safety profile that could prevent regulatory approval, prevent market acceptance, limit their commercial potential or result in significant negative consequences.

If our product candidates are associated with undesirable adverse events or have unexpected characteristics in preclinical studies or clinical trials when used alone or in combination with other approved products or investigational new drugs we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable adverse events or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Treatment-related adverse events could also affect patient recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. Any of these occurrences may prevent us from achieving or maintaining market acceptance of the affected product candidate and may harm our business, financial condition and prospects significantly. It is likely that there will be adverse events associated with the use of our product candidates as is typically the case with oncology drugs. Results of our studies or trials could reveal a high and unacceptable severity and prevalence of these or other adverse events. In such an event, our trials could be suspended or terminated and the FDA, EMA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our product candidates for any or all targeted indications. Drug-related adverse events could also affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

In addition, our product candidates may be used in populations for which safety concerns may be particularly scrutinized by regulatory authorities. Our product candidates may be studied in combination with other therapies, which may exacerbate adverse events associated with the therapy. Patients treated with our product candidates may also be undergoing surgical, radiation and chemotherapy treatments, which can cause adverse events that are unrelated to our product candidates but may still impact the success of our clinical trials. The inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or due to the gravity of such patients' illnesses. For example, it is expected that some of the patients to be enrolled in our current or future clinical trials may die or experience major clinical events either during the course of our clinical trials or after participating in such trials for non-treatment related reasons.

If significant adverse events are observed in any of our current or future clinical trials, we may have difficulty recruiting patients to the clinical trials, patients may drop out of our trials, or we may be required to abandon the

trials or our development efforts of that product candidate altogether. We, the FDA, EMA, other comparable foreign regulatory authorities or an IRB may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse events. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage trials have later been found to cause adverse events that prevented their further development. Even if the adverse events do not preclude the product candidate from obtaining or maintaining marketing approval, undesirable adverse events may inhibit market acceptance due to its tolerability versus other therapies. Any of these developments could materially harm our business, financial condition and prospects. Further, if any of our product candidates obtains marketing approval, toxicities associated with such product candidates previously not seen during clinical testing may also develop after such approval and lead to a requirement to conduct additional clinical safety trials, additional contraindications, warnings and precautions being added to the drug label, significant restrictions on the use of the product or the withdrawal of the product from the market. We cannot predict whether our product candidates will cause toxicities in humans that would preclude or lead to the revocation of regulatory approval based on preclinical studies or early stage clinical trials.

Interim, topline and preliminary data from our preclinical studies and clinical trials that we announce or publish from time to time may change as more 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 preclinical studies and clinical trials. These interim 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. For example, we may report responses in certain patients that are unconfirmed at the time and which do not ultimately result in confirmed responses to treatment after follow-up evaluations. 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 trials, 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. 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. Adverse changes between 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 Class A common stock.

In addition, the information we choose to publicly disclose regarding a particular study or trial is typically selected from a more extensive amount of available information. Investors may not agree with what we determine is the material or otherwise appropriate information to include in our public disclosures, 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 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 of our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

If we experience delays or difficulties in the enrollment or maintenance of patients in clinical trials, our regulatory submissions or receipt of necessary marketing approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials to such trial's conclusion as required by the FDA, EMA or other comparable foreign regulatory authorities. Patient enrollment is a significant factor in the timing of clinical trials. Our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. We will utilize genomic profiling of patients' tumors to identify suitable patients for

recruitment into our clinical trials for NVL-520 and NVL-655. For these product candidates, we seek patients with specific genomic alterations that our product candidates are designed to precisely target. We cannot be certain (i) how many patients will have the requisite genomic alterations that qualify for inclusion in our clinical trials, (ii) that the number of patients enrolled in each program will suffice for regulatory approval or (iii) if regulatory approval is obtained, whether each specific ROS1 fusion or ALK fusion will be included in the approved drug label. Additionally, we face competition, including from large pharmaceutical companies with significantly more resources than us, for enrollment of our precisely target patient population, which may impact our ability to successfully recruit patients for our clinical trials. If our strategies for patient identification and enrollment prove unsuccessful, we may have difficulty enrolling or maintaining patients appropriate for our product candidates.

Our ability to enroll patients may also be significantly delayed by the evolving COVID-19 pandemic and we do not know the extent and scope of such delays at this point. In addition, patients may not be able or willing to visit clinical trial sites for dosing or data collection purposes due to limitations on travel and physical distancing imposed or recommended by federal or state governments or patients' reluctance to visit the clinical trial sites during the pandemic. These and other factors resulting from the COVID-19 pandemic could delay our clinical trials and our regulatory submissions.

Patient enrollment may be affected if our competitors have ongoing clinical trials for programs that are under development for the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials instead enroll in clinical trials of our competitors' programs. Patient enrollment for our current or future clinical trials may be affected by other factors, including:

- size and nature of the patient population;
- severity of the disease under investigation;
- availability and efficacy of approved drugs for the disease under investigation;
- patient eligibility criteria for the trial in question as defined in the protocol, including biomarker-driven identification and/or certain highly-specific criteria related to stage of disease progression, which may limit the patient populations eligible for our clinical trials to a greater extent than competing clinical trials for the same indication that do not have a biomarker-driven patient eligibility criteria;
- perceived risks and benefits of the product candidate under study;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new products that may be approved or other product candidates being investigated for the indications we are investigating;
- clinicians' willingness to screen their patients for biomarkers to indicate which patients may be eligible for enrollment in our clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- proximity and availability of clinical trial sites for prospective patients; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion or, because they may be late-stage cancer patients, will not survive the full terms of the clinical trials.

Our inability to enroll 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 for our product candidates and jeopardize our ability to obtain marketing approval for the sale of our product candidates. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining participation in our clinical trials through the treatment and any follow-up periods.

We have never commercialized a product candidate as a company before and currently lack the necessary expertise, personnel and resources to successfully commercialize any products on our own or together with suitable collaborators.

We have never commercialized a product candidate as a company. We may license certain rights with respect to our product candidates to collaborators, and, if so, we will rely on the assistance and guidance of those collaborators. For product candidates for which we retain commercialization rights and marketing approval, we will have to develop our own sales, marketing and supply organization or outsource these activities to a third party.

Factors that may affect our ability to commercialize our product candidates, if approved, on our own include recruiting and retaining adequate numbers of effective sales and marketing personnel, developing adequate educational and marketing programs to increase public acceptance of our approved product candidates, ensuring regulatory compliance of our company, employees and third parties under applicable healthcare laws, and other unforeseen costs associated with creating an independent sales and marketing organization. Developing a sales and marketing organization will be expensive and time-consuming and could delay the launch of our product candidates upon approval. We may not be able to build an effective sales and marketing organization. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of our product candidates, we may not generate revenues from them or be able to reach or sustain profitability.

The ongoing COVID-19 pandemic could adversely impact our business, including our clinical trials and preclinical studies.

The ongoing COVID-19 pandemic could adversely impact our business, including our clinical trials and preclinical studies. National, state and local governments have implemented and may continue to implement safety precautions, including quarantines, border closures, increased border controls, travel restrictions, shelter in place orders and shutdowns and other measures. These measures may disrupt normal business operations and may have significant negative impacts on businesses and financial markets worldwide. As the ongoing COVID-19 pandemic continues to spread around the globe and new variants of the virus continue to emerge, we may experience disruptions that could severely impact our business and clinical trials, including:

- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays or difficulties in enrolling and retaining patients in any clinical trials, particularly elderly subjects, who are at a higher risk of severe illness or death from COVID-19;
- difficulties interpreting data from our clinical trials due to the possible effects of COVID-19 on patients;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others;
- interruption or delays in the operations of the FDA, EMA or other regulatory authorities, which may impact review and approval timelines;
- limitations in resources that would otherwise be focused on the conduct of our business, our preclinical studies or our clinical trials, including because of sickness or the desire to avoid contact with large groups of people or as a result of government-imposed “shelter in place” or similar working restrictions;
- interruptions, difficulties or delays arising in our existing operations and company culture as a result of the majority of our employees working remotely, including those hired during the COVID-19 pandemic;
- delays in receiving approval from regulatory authorities to initiate our clinical trials;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials;

- interruptions in preclinical studies due to restricted or limited operations at the CROs conducting such studies;
- interruption in global freight and shipping that may affect the transport of clinical trial materials, such as investigational drug product to be used in our clinical trials;
- changes in regulations as part of a response to the ongoing COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, or to discontinue the clinical trials altogether, or which may result in unexpected costs;
- delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel; and
- refusal of the FDA, EMA or other regulatory authorities to accept data from clinical trials in affected geographies outside of their respective jurisdictions.

We are continuing to assess the impact that the ongoing COVID-19 pandemic may have on our ability to effectively conduct our business operations as planned and there can be no assurance that we will be able to avoid a material impact on our business from the spread of COVID-19 or its consequences, including disruption to our business and downturns in business sentiment generally or in our industry or due to shutdowns that may be requested or mandated by federal, state and local governmental authorities. As a result of the COVID-19 pandemic, our employees are currently telecommuting, which may impact certain of our operations over the near term and long term.

Additionally, certain third parties with whom we engage or may engage, including collaborators, contract organizations, third-party manufacturers, suppliers, clinical trial sites, regulators and other third parties have similarly adjusted their operations and have and are continuing to assess their capacity in light of the COVID-19 pandemic. If these third parties experience shutdowns or continued business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively impacted. For example, as a result of the COVID-19 pandemic, there could be delays in the procurement of materials or manufacturing supply chain for one or more of our product candidates, which could delay or otherwise impact our preclinical studies and our clinical trials. Additionally, all of our preclinical studies and our clinical trial are conducted by CROs, which could be discontinued or delayed as a result of the pandemic. It is also likely that the disproportionate impact of COVID-19 on hospitals and clinical sites will have an impact on recruitment and retention for our clinical trials. In addition, certain clinical trial sites for product candidates similar to ours have experienced, and others may experience in the future, delays in collecting, receiving and analyzing data from patients enrolled in clinical trials due to limited staff at such sites, limitation or suspension of on-site visits by patients, or patients' reluctance to visit the clinical trial sites during the pandemic and we may experience similar delays. CROs have also made certain adjustments to the operation of such trials in an effort to ensure the monitoring and safety of patients and minimize risks to trial integrity during the pandemic in accordance with the guidance issued by the FDA and may need to make further adjustments in the future that could impact the timing or enrollment of our clinical trials. Many of these adjustments are new and untested, may not be effective, may increase costs, and may have unforeseen effects on the enrollment, progress and completion of these trials and the findings from these trials. We may experience delays in the completion of our preclinical studies and clinical trials, the initiation of our planned clinical trials, and in patient selection, enrollment, and the progression of other activities related to our ongoing and planned clinical trials. We may need to suspend our clinical trials and may encounter other negative impacts to such trials due to the effects of the COVID-19 pandemic.

We may be required to develop and implement additional clinical trial policies and procedures designed to help protect subjects from COVID-19. For example, in March 2020, the FDA issued a guidance, which the FDA subsequently updated several times, on conducting clinical trials during the pandemic, which describes a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical trial report contingency measures implemented to manage the clinical trial, and any disruption of the clinical trial as a result of the COVID-19 pandemic; a list of all subjects affected by the COVID-19 pandemic related study disruption by unique subject identifier and by investigational site and a description of how the

individual's participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (i.e., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the clinical trial. In June 2020, the FDA also issued a guidance on good manufacturing practice considerations for responding to COVID-19 infection in employees in drug products manufacturing, including recommendations for manufacturing controls to prevent contamination of drugs.

Furthermore, the COVID-19 pandemic may also impact the timelines of FDA regulatory inspections and reviews. Since March 2020 when foreign and domestic inspections were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections. As of May 2021, certain inspections, such as foreign preapproval, surveillance, and for-cause inspections that are not deemed mission-critical, remain temporarily postponed. In April 2021, the FDA issued guidance for industry formally announcing plans to employ remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates and in May 2021 announced plans to continue progress toward resuming standard operational levels. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue a complete response letter or defer action on the application until an inspection can be completed Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. Additionally, as of March 18, 2021, the FDA noted it is continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions the FDA is unable to complete such required inspections during the review period. To the extent any such events impact the operations of any of our third parties, our development activities may be negatively affected.

The global outbreak of COVID-19 continues to rapidly evolve. While the extent of the impact of the current COVID-19 pandemic on our business and financial results is uncertain, a continued and prolonged public health crisis such as the COVID-19 pandemic could have a material negative impact on our business, financial condition and operating results.

To the extent the ongoing COVID-19 pandemic adversely affects our business, financial condition and operating results, it may also have the effect of heightening many of the risks described in this "Risk Factors" section.

We have limited resources and are currently focusing our efforts on the development of NVL-520 and NVL-655 in particular indications and advancing our discovery programs. As a result, we may fail to capitalize on other indications or product candidates that may ultimately have proven to be more profitable.

We are currently focusing our resources and efforts on our lead product candidates, NVL-520 and NVL-655, for advanced ROS1-positive NSCLC and other solid tumors and advanced ALK-positive NSCLC and other solid tumors, respectively, and advancing our ALK IXDN, HER2 and other discovery programs. As a result, because we have limited resources, we may forgo or delay pursuit of opportunities for other indications or with other product candidates that may 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 activities for NVL-520 and NVL-655 and our discovery programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target markets for NVL-520 and NVL-655 and any future product candidates we identify through our discovery programs, we may enter into collaboration, licensing or other strategic arrangements with the effect of relinquishing valuable rights in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

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

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates. Our competitors have developed, are developing or may develop products, product candidates and processes competitive with our product candidates. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of product candidates are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may attempt to develop product candidates. In addition, our product candidates may need to compete with drugs physicians use off-label to treat the indications for which we seek approval. This may make it difficult for us to replace existing therapies with our product candidates.

In particular, there is intense competition in the field of oncology. We have competitors both in the U.S. and internationally, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, emerging and start-up companies, universities and other research institutions. We also compete with these organizations to recruit and retain qualified scientific and management personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We expect to face competition from existing products and products in development for each of our lead programs and in particular, our competitors that are developing product candidates often have the advantage of significant financial resources. For NVL-520, there are currently two ROS1-targeted kinase inhibitors approved for use in first-line, TKI naïve ROS1-positive NSCLC: crizotinib and entrectinib. Ceritinib is also recommended for use in ROS1-positive NSCLC patients according to NCCN guidelines. Pfizer's lorlatinib is a dual ALK/ROS1 inhibitor that is in development for the treatment of ROS1-positive NSCLC. This product has received marketing approval for the treatment of ALK-positive NSCLC, and has demonstrated CNS activity as reported in its prescribing information. Repotrectinib is a dual TRK/ROS1 inhibitor that is in development and has demonstrated clinical activity in ROS1-positive NSCLC patients but also retains potent TRK inhibition at clinically relevant concentrations. AnHeart Therapeutics' taletrectinib is a dual TRK/ROS1 inhibitor and is in development for patients with ROS1-positive NSCLC. For NVL-655, there are five currently approved ALK inhibitors for the treatment of ALK-positive NSCLC: crizotinib, lorlatinib, ceritinib, alectinib, and brigatinib. All five have line-agnostic approvals for the treatment of ALK-positive NSCLC patients, including for patients who are TKI naïve. Additionally, lorlatinib has demonstrated activity in patients that have progressed on crizotinib, alectinib, or ceritinib.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources, established presence in the market, and expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. Large pharmaceutical and biotechnology companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and manufacturing biotechnology product candidates. These companies also have significantly greater research and marketing capabilities than we do and may also have product candidates that have been approved or are in late stages of development, and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical and biotechnology companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies, as well as in acquiring technologies complementary to, or necessary for, our programs. As a result of all of these factors, our competitors may succeed in obtaining approval from the FDA, EMA or other comparable foreign regulatory authorities or in discovering, developing and commercializing product candidates in our field before we do.

Our potential commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe adverse events, are more convenient, have a broader label, are marketed more effectively, are more widely reimbursed or are less expensive than any products that we may develop. Physicians may be more willing to prescribe our competitors' products for various reasons, and may rely on guidelines related to treatment of patients issued by medical societies, industry groups or other organizations, which may not include, and may never include, our products. Our competitors also may obtain marketing approval from the FDA, EMA or other comparable foreign regulatory authorities for their products 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 or make our development and marketing more complicated. Even if the product candidates we develop achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness. Technological advances or products developed by our competitors may render our technologies or product candidates obsolete, less competitive or not economical. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our products we may develop, if approved, could be adversely affected.

The manufacture of drugs is complex, and our third-party manufacturers may encounter difficulties in production. If any of our third-party manufacturers encounter such difficulties, our ability to provide adequate supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or prevented.

Manufacturing drugs, especially in large quantities, is complex and may require the use of innovative technologies. Each lot of an approved drug product must undergo thorough testing for identity, strength, quality, purity and potency. Manufacturing drugs requires facilities specifically designed for and validated for this purpose, as well as sophisticated quality assurance and quality control procedures. Slight deviations anywhere in the manufacturing process, including filling, labelling, packaging, storage and shipping and quality control and testing, may result in lot failures, product recalls or spoilage. When changes are made to the manufacturing process, we may be required to provide preclinical and clinical data showing the comparable identity, strength, quality, purity or potency of the products before and after such changes. If microbial, viral or other contaminations are discovered at the facilities of our manufacturer, such facilities may need to be closed for an extended period of time to investigate and remedy the contamination, which could delay clinical trials and adversely harm our business. Contaminations can also lead to allegations of harm, including infections or allergic reactions, or closure of product facilities due to possible contamination.

If our third-party manufacturers are unable to produce sufficient quantities for clinical trials or for commercialization as a result of these challenges, or otherwise, our development and commercialization efforts would be impaired, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates progress through preclinical and clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize yield and manufacturing batch size, minimize costs and achieve consistent quality and results. For example, we may introduce an alternative formulation of one or more of our product candidates during the course of our clinical trials. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commercialize our product candidates, if approved, and impair our ability to generate revenue.

Our product candidates may not achieve adequate market acceptance among physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Even if our product candidates receive regulatory approval, they may not gain adequate market acceptance among physicians, patients, third-party payors and others in the medical community. The degree of market acceptance of any of our approved product candidates will depend on a number of factors, including:

- the efficacy and safety profile as demonstrated in clinical trials compared to alternative treatments;
- the timing of market introduction of the product candidate as well as competitive products;
- the clinical indications for which a product candidate is approved;
- restrictions on the use of product candidates in the labelling approved by regulatory authorities, such as boxed warnings or contraindications in labelling, or a Risk Evaluation and Mitigation Strategy (REMS), if any, which may not be required of alternative treatments and competitor products;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the cost of treatment in relation to alternative treatments;
- the availability of coverage and adequate reimbursement by third-party payors, including government authorities;
- willingness of physicians to use our product candidates, if approved, in lieu of (or as a second-line treatment in conjunction with) other approved therapies;
- the availability of an approved product candidate for use as a combination therapy;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and undergo required diagnostic screening to determine treatment eligibility and of physicians to prescribe these therapies and diagnostic tests;
- the effectiveness of sales and marketing efforts;
- unfavorable publicity relating to our product candidates; and
- the approval of other new therapies for the same indications.

If any of our product candidates are approved but do not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors and patients, we may not generate or derive sufficient revenue from that product candidate and our financial results could be negatively impacted.

The market opportunities for any product candidates we develop, if approved, may be limited to certain smaller patient subsets and may be smaller than we estimate them to be.

When cancer is detected early (referred to as localized disease), conventional treatments which include chemotherapy, hormone therapy, surgery and radiation therapy and/or selected targeted therapies may be adequate to cure the patient in many cases. However, once cancer has spread to other areas (advanced or metastatic disease), cancer treatments may not be sufficient to provide a cure but often can significantly prolong life without curing the cancer. First-line therapies designate treatments that are initially administered to patients with advanced or metastatic disease, while second- and third-line therapies are administered to patients when the prior therapies lose their effectiveness. The FDA, EMA and other regulatory bodies often approve cancer therapies for a particular line of treatment. Typically, drug approvals are initially granted for use in later lines of treatment, but with additional evidence of significant efficacy from clinical trials, biopharmaceutical companies can successfully seek and gain approval for use in earlier lines of treatment.

We plan to initially seek approval of NVL-520, NVL-655 and any other future product candidates in most instances for previously treated patients with advanced or metastatic cancer where at least one prior therapy has limited clinical benefit or where tumors have developed resistance to such therapy. For those product candidates that prove to be sufficiently safe and effective, if any, we would potentially expect to seek approval ultimately as

a first line TKI therapy. There is no guarantee that our product candidates, even if approved for previously treated patients would be approved for an earlier line of therapy, and prior to any such approvals we may have to conduct additional clinical trials that may be costly, time-consuming and subject to risk.

Our projections of both the number of people who have the cancers we are targeting, as well as the subset of people with these cancers in a position to receive a particular line of therapy and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new data and studies may change the estimated incidence or prevalence of the cancers that we are targeting, especially if new therapies that are approved while we advance our product candidates affect the treatment paradigm and/or the size of the target population. The potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. Consequently, even if our product candidates are approved, the number of patients that may be eligible for treatment with our product candidates may turn out to be much lower than expected. In addition, we have not yet conducted market research to determine how treating physicians would expect to prescribe a product that is approved for multiple tumor types if there are different lines of approved therapies for each such tumor type. Even if we obtain significant market share for our products, if approved, if the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

Any product candidates we develop may become subject to unfavorable third-party coverage and reimbursement practices, as well as pricing regulations.

Patients rely on insurance coverage by third-party payors (third-party payors include Medicare and Medicaid (government payors) and commercial insurance companies such as Blue Cross Blue Shield, Humana, Cigna, etc.), to pay for products. The availability and extent of coverage and adequate reimbursement by third-party payors, including government health administration authorities, private health coverage insurers, managed care organizations and other third-party payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the U.S. and internationally, on the extent to which the costs of such product candidates will be covered and reimbursed by third-party payors. No uniform policy exists for coverage and reimbursement in the U.S. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize an adequate return on our investment. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not successfully commercialize any product candidate for which we obtain marketing approval.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved products. In the U.S., for example, principal decisions about reimbursement for new products are typically made by the CMS, an agency within the HHS. CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare, and private third-party payors often follow CMS's decisions regarding coverage and reimbursement to a substantial degree. However, one third-party payor's determination to provide coverage for a product candidate does not assure that other payors will also provide coverage for the product candidate. As a result, the coverage determination process is often time-consuming and costly. Factors payors consider in determining reimbursement are based on whether the product is: (i) a covered benefit under its health plan; (ii) safe, effective and medically necessary; (iii) appropriate for the specific patient; (iv) cost-effective; and (v) neither experimental nor investigational. This process will require us to provide scientific and clinical support for the use of our products to each third-party payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

As federal and state governments implement additional health care cost containment measures, including measures to lower prescription drug pricing, we cannot be sure that our products, if approved, will be covered by private or public payors, and if covered, whether the reimbursement will be adequate or competitive with other marketed products. For example, former President Trump previously signed executive orders aimed at lowering

prescription drug prices. Such other actions by federal and state governments and health plans may put additional downward pressure on pharmaceutical pricing and health care costs, which could negatively impact coverage and reimbursement for our products if approved, our revenue, and our ability to compete with other marketed products and to recoup the costs of our research and development. For further discussion, see "*— Current and future legislation may increase the difficulty and cost for us to obtain reimbursement for our product candidates;*" and "*— The prices of prescription pharmaceuticals in the U.S. and foreign jurisdictions are the subject of considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed for marketing.*"

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. Further, such payors are increasingly challenging the price, examining the medical necessity and reviewing the cost effectiveness of medical product candidates. There may be especially significant delays in obtaining coverage and reimbursement for newly approved drugs. Third-party payors may limit coverage to specific product candidates on an approved list, known as a formulary, which might not include all FDA-approved drugs for a particular indication. We may need to conduct expensive pharmaco-economic studies to demonstrate the medical necessity and cost effectiveness of our products. Nonetheless, our product candidates may not be considered medically necessary or cost effective. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be.

In addition, companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or products, will apply to companion diagnostics. Additionally, if any companion diagnostic provider is unable to obtain reimbursement or is inadequately reimbursed, that may limit the availability of such companion diagnostic, which would negatively impact prescriptions for our product candidates, if approved.

Outside the U.S., the commercialization of therapeutics is generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the EU, medical product prices are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after a product receives marketing approval. 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 general, product prices under such systems are substantially lower than in the U.S. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the U.S., the reimbursement for our products may be reduced compared with the U.S. and may be insufficient to generate commercially reasonable revenue and profits.

If we are unable to establish or sustain coverage and adequate reimbursement for any product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. Coverage policies and third-party payor reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Our business entails a significant risk of product liability and if we are unable to obtain sufficient insurance coverage such inability could have an adverse effect on our business and financial condition.

Our business exposes us to significant product liability and other risks inherent in the development, testing, manufacturing and marketing of therapeutic treatments. Product liability and other claims or incidents, such as cyber incidents and breaches, could delay or prevent completion of our development programs. If we succeed in marketing products, such claims could result in an FDA, EMA or other regulatory authority investigation of the

safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs. FDA, EMA or other regulatory authority investigations could potentially lead to a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources and substantial monetary awards to trial participants or patients. We currently have product liability and other insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to advancing our product candidates into clinical trials or marketing any of our product candidates, if approved. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial, product liability, and other types of insurance (such as cyber insurance) is becoming increasingly expensive and difficult to obtain. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability or other claims or incidents, including data breach and incidents, that could have an adverse effect on our business and financial condition.

Risks related to regulatory approval and other legal compliance matters

We may be unable to obtain U.S. or foreign regulatory approval and, as a result, may be unable to commercialize our product candidates.

Our product candidates are and will continue to be subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labelling, storage, packaging, advertising and promotion, pricing, marketing and distribution of drugs. Rigorous preclinical testing and clinical trials and an extensive regulatory approval process must be successfully completed in the U.S. and in many foreign jurisdictions before a new drug can be approved for marketing. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. We cannot provide any assurance that any product candidate we may develop will progress through required clinical testing and obtain the regulatory approvals necessary for us to begin selling them.

We have not conducted, managed or completed large-scale or pivotal clinical trials nor managed the regulatory approval process with the FDA, EMA or any other regulatory authority. The time required to obtain approvals from the FDA, EMA and other regulatory authorities is unpredictable and requires successful completion of extensive clinical trials which typically takes many years, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when evaluating clinical trial data can, and often does, change during drug development, which makes it difficult to predict with any certainty how they will be applied. We may also encounter unexpected delays or increased costs due to new government regulations, including future legislation or administrative action, or changes in applicable FDA, EMA or other regulatory policy during the period of drug development, clinical trials and regulatory review.

Applications for our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other comparable foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials;
- the FDA, EMA or other comparable foreign regulatory authorities may determine that our product candidates are not safe and effective or have undesirable or unintended adverse events, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- the FDA, EMA or other comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- we may be unable to demonstrate to the FDA, EMA or other comparable foreign regulatory authorities that our product candidate's risk-benefit ratio for its proposed indication is acceptable;

- the FDA, EMA or other comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or other comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Any delay or failure in seeking or obtaining required approvals would have a material and adverse effect on our ability to generate revenue from any particular product candidates we are developing and for which we are seeking approval. Furthermore, any regulatory approval to market a drug may be subject to significant limitations on the approved uses or indications for which we may market, promote and advertise the drug or the labelling or other restrictions. In addition, the FDA has the authority to require a REMS plan as part of approving a NDA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. These requirements or restrictions might include limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. These limitations and restrictions may significantly limit the size of the market for the drug and affect reimbursement by third-party payors.

We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process varies among countries, and generally includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Moreover, the time required to obtain approval may differ from that required to obtain FDA approval.

We may develop our current or future product candidates in combination with other therapies, which would expose us to additional risks.

We may develop our current or future product candidates in combination with one or more currently approved cancer therapies or therapies in development. Even if any of our current or future product candidates were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA, EMA or other comparable foreign regulatory authorities could revoke approval of the therapy used in combination with any of our product candidates, or safety, efficacy, manufacturing or supply issues could arise with these existing therapies. In addition, it is possible that existing therapies with which our product candidates are approved for use could themselves fall out of favor or be relegated to later lines of treatment. This could result in the need to identify other combination therapies for our product candidates or our own products being removed from the market or being less successful commercially.

We may also evaluate our current or future product candidates in combination with one or more other cancer therapies that have not yet been approved for marketing by the FDA, EMA or comparable foreign regulatory authorities. We will not be able to market and sell any product candidate in combination with any such unapproved cancer therapies that do not ultimately obtain marketing approval.

If the FDA, EMA or other comparable foreign regulatory authorities do not approve or withdraw their approval of these other therapies, or if safety, efficacy, commercial adoption, manufacturing or supply issues arise with the therapies we choose to evaluate in combination with any of our current or future product candidates, we may be unable to obtain approval of or successfully market any one or all of the current or future product candidates we develop. Additionally, if the third-party providers of therapies or therapies in development used in combination with our current or future product candidates are unable to produce sufficient quantities for clinical trials or for commercialization of our current or future product candidates, or if the cost of combination therapies are prohibitive, our development and commercialization efforts would be impaired, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

The FDA, EMA and other comparable foreign regulatory authorities may not accept data from trials conducted in locations outside of their jurisdiction.

We anticipate we will initially conduct clinical trials of our product candidates in the U.S. and we may choose to conduct our clinical trials internationally as well. The acceptance of study data by the FDA, EMA or other comparable foreign regulatory authority from clinical trials conducted outside of their respective jurisdictions may be subject to certain conditions. In cases where data from U.S. clinical trials are intended to serve as the basis for marketing approval in the foreign countries outside the U.S., the standards for clinical trials and approval may be different. There can be no assurance that any U.S. or foreign regulatory authority would accept data from trials conducted outside of its applicable jurisdiction. If the FDA, EMA or any applicable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction. For example, even if the FDA or EMA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion and reimbursement of the product candidate in those countries. However, a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the U.S., including additional preclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the U.S., a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and establishing and maintaining compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we or any future collaborator fail to comply with the regulatory requirements in international markets or fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our potential product candidates will be harmed.

Additionally, on June 23, 2016, the electorate in the U.K. voted in favor of leaving the EU (Brexit). Following protracted negotiations, the U.K. left the EU on January 31, 2020, and a transition period to December 31, 2020, was established to allow the U.K. and the EU to negotiate the U.K.'s withdrawal. As a result, effective January 1, 2021, the U.K. is no longer part of the European Single Market and EU

Customs Union. A co-operation agreement was signed between the U.K. and the EU in December 2020, which was applied provisionally beginning on January 1, 2021, and entered into force on May 1, 2021. The agreement addresses trade, economic arrangements, law enforcement, judicial cooperation, and a governance framework including procedures for dispute resolution, among other things. As both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal.

Since the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, the consequences of Brexit and the impact the future regulatory regime that applies to products and the approval of product candidates in the U.K. remains unclear. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency (MHRA) became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland, and Wales under domestic law, whereas Northern Ireland will continue to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916)

(as amended) (HMR) as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of EU law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the U.K. for our product candidates, which could significantly and materially harm our business.

Even if our product candidates receive regulatory approval, they will be subject to significant post-marketing regulatory requirements and oversight.

Any regulatory approvals that we may receive for our product candidates will require the submission of reports to regulatory authorities and on-going surveillance to monitor the safety and efficacy of the product candidate, may contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, and may include burdensome post-approval study or risk management requirements and regulatory inspection. For example, the FDA may require a REMS in order to approve our product candidates, which could entail requirements for a medication guide, physician training and communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA, EMA or foreign regulatory authorities approve our product candidates, the manufacturing processes, labelling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export and recordkeeping for our product candidates will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as on-going compliance with cGMPs and good clinical practices ("GCP") for any clinical trials that we conduct post-approval. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA, EMA and other regulatory authorities for compliance with cGMP regulations and standards. If we or a regulatory authority discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facilities where the product is manufactured, a regulatory authority may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. In addition, failure to comply with FDA, EMA and other comparable foreign regulatory requirements may subject our company to administrative or judicially imposed sanctions, including:

- delays in or the rejection of product approvals;
- restrictions on our ability to conduct clinical trials, including full or partial clinical holds on ongoing or planned trials;
- restrictions on the products, manufacturers or manufacturing process;
- warning or untitled letters;
- civil and criminal penalties;
- injunctions;
- suspension or withdrawal of regulatory approvals;
- product seizures, detentions or import bans;
- voluntary or mandatory product recalls and publicity requirements;
- total or partial suspension of production;
- imposition of restrictions on operations, including costly new manufacturing requirements;
- revisions to the labelling, including limitation on approved uses or the addition of additional warnings, contraindications or other safety information, including boxed warnings;
- imposition of a REMS, which may include distribution or use restrictions; and
- requirements to conduct additional post-market clinical trials to assess the safety of the product.

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

The FDA, EMA and other regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off-label uses.

If any of our product candidates are approved and we are found to have improperly promoted off-label uses of those products, we may become subject to significant liability. The FDA, EMA and other regulatory authorities strictly regulate the promotional claims that may be made about prescription products, such as our product candidates, if approved. In particular, a product may not be promoted in the U.S. for uses that are not approved by the FDA as reflected in the product's approved labelling, or in other jurisdictions for uses that differ from the labelling or uses approved by the applicable regulatory authorities. While physicians may prescribe products for off-label uses, the FDA, EMA and other regulatory authorities actively enforce laws and regulations that prohibit the promotion of off-label uses by companies, including promotional communications made by companies' sales force with respect to off-label uses that are not consistent with the approved labelling, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties. If we are found to have promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

If we are required by the FDA, EMA or comparable regulatory authority to obtain clearance or approval of a companion diagnostic test in connection with approval of any of our product candidates or a group of therapeutic products, and we do not obtain or we face delays in obtaining clearance or approval of a diagnostic test, we may not be able to commercialize the product candidate and our ability to generate revenue may be materially impaired.

If we are required by the FDA, EMA or a comparable regulatory authority to obtain clearance or approval of a companion diagnostic test in connection with approval of any of our product candidates, such companion diagnostic test would be used during our more advanced phase clinical trials as well as in connection with the commercialization of our product candidates. To be successful in developing and commercializing product candidates in combination with these companion diagnostics, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to ensuring the safe and effective use of a novel therapeutic product or new indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared. In certain circumstances (for example, when a therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory available therapy exists or when the labelling of an approved product needs to be revised to address a serious safety issue), however, the FDA may approve a therapeutic product without the prior or contemporaneous marketing authorization of a companion diagnostic. In this case, approval of a companion diagnostic may be a post-marketing requirement or commitment.

Co-development of companion diagnostics and therapeutic products is critical to the advancement of precision medicine. Whether initiated at the outset of development or at a later point, co-development should generally be conducted in a way that will facilitate obtaining contemporaneous marketing authorizations for the therapeutic product and the associated companion diagnostic. If a companion diagnostic is required to identify patients who are most likely to benefit from receiving the product, to be at increased risk for serious adverse events as a result

of treatment with a particular therapeutic product, or to monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness, then the FDA has required marketing approval of all companion diagnostic tests essential for the safe and effective use of a therapeutic product for cancer therapies. Various foreign regulatory authorities also regulate in vitro companion diagnostics as medical devices and, under those regulatory frameworks, will likely require the conduct of clinical trials to demonstrate the safety and effectiveness of any future diagnostics we may develop, which we expect will require separate regulatory clearance or approval prior to commercialization in those countries.

The approval of a companion diagnostic as part of the therapeutic product's labelling limits the use of the therapeutic product to only those patients who express the specific genomic alteration or mutation alteration that the companion diagnostic was developed to detect. If the FDA, EMA or a comparable regulatory authority requires clearance or approval of a companion diagnostic for any of our product candidates, whether before, concurrently with approval, or post-approval of the product candidate, we, and/or future collaborators, may encounter difficulties in developing and obtaining clearance or approval for these companion diagnostics. Any delay or failure by us or third-party collaborators to develop or obtain regulatory clearance or approval of a companion diagnostic could delay or prevent approval or continued marketing of our related product candidates. Further, in April 2020, the FDA issued new guidance on developing and labelling companion diagnostics for a specific group of oncology therapeutic products, including recommendations to support a broader labelling claim rather than individual therapeutic products. We will continue to evaluate the impact of this guidance on our companion diagnostic development and strategy. This guidance and future issuances from the FDA, EMA and other regulatory authorities may impact our development of a companion diagnostic for our product candidates and could result in delays in regulatory clearance or approval or a change in the determination for whether or not a companion diagnostic is still required for our product candidates. We may be required to conduct additional studies to support a broader claim or more narrowed claim for a subset population. Also, to the extent other approved diagnostics are able to broaden their labelling claims to include any of our future approved product candidates covered indications, we may no longer need to continue our companion diagnostic development plans or we may need to alter those companion diagnostic development strategies, which could adversely impact our ability to generate revenue from the sale of our companion diagnostic test.

Additionally, we may rely on third parties for the design, development and manufacture of companion diagnostic tests for our product candidates. If we enter into such collaborative agreements, we will be dependent on the sustained cooperation and effort of our future collaborators in developing and obtaining clearance or approval for these companion diagnostics. It may be necessary to resolve issues such as selectivity/specificity, analytical validation, reproducibility, or clinical validation of companion diagnostics during the development and regulatory clearance or approval processes. Moreover, even if data from preclinical studies and early clinical trials appear to support development of a companion diagnostic for a product candidate, data generated in later clinical trials may fail to support the analytical and clinical validation of the companion diagnostic. We and our future collaborators may encounter difficulties in developing, obtaining regulatory clearance or approval for, manufacturing and commercializing companion diagnostics similar to those we face with respect to our product candidates themselves, including issues with achieving regulatory clearance or approval, production of sufficient quantities at commercial scale and with appropriate quality standards, and in gaining market acceptance. If we are unable to successfully develop companion diagnostics for our product candidates, or experience delays in doing so, the development of our product candidates may be adversely affected, our product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of our product candidates that obtain marketing approval. As a result, our business, results of operations and financial condition could be materially harmed. In addition, a diagnostic company with whom we contract may decide to discontinue selling or manufacturing the companion diagnostic test that we anticipate using in connection with development and commercialization of product candidates or our relationship with such diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the co-development or commercialization of our companion diagnostic and therapeutic product candidates.

Where appropriate, we plan to pursue approval from the FDA, EMA or comparable foreign regulatory authorities through the use of accelerated registration pathways. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, EMA or comparable regulatory authorities, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA, EMA or such other regulatory authorities may seek to withdraw accelerated approval.

Where appropriate, we plan to pursue accelerated development strategies in areas of medical need. We may seek an accelerated approval pathway for our one or more of our product candidates from the FDA, EMA or comparable foreign regulatory authorities. Under the accelerated approval provisions in the FDCA, and the FDA's implementing regulations, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. If such post-approval studies fail to confirm the drug's clinical benefit, the FDA may withdraw its approval of the drug.

Prior to seeking accelerated approval, we will seek feedback from the FDA, EMA or comparable foreign regulatory authorities and will otherwise evaluate our ability to seek and receive such accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent feedback from the FDA, EMA or comparable foreign regulatory authorities, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or under another expedited regulatory designation (i.e., Fast Track designation, Breakthrough Therapy designation or orphan drug designation), there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA, EMA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidate would result in a longer time period to commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

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

We may seek certain designations for one or more of our product candidates that could expedite review and approval by the FDA. A Breakthrough Therapy product is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious condition, and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For

products that have been designated as Breakthrough Therapies, early and frequent interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development.

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

We may also seek a priority review designation for one or more of our product candidates. If the FDA determines that a product candidate intended to treat a serious condition and, if approved, offers a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation shortens the goal for the FDA to review an application within six months, rather than the standard review period of ten months.

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

In the EU, we may seek PRIME for some of our product candidates in the future. PRIME is a voluntary program launched by the EMA that is aimed at enhancing the scientific and regulatory support for the development and accelerated assessment of new product candidates that target an unmet medical need. PRIME is aimed to offer early and proactive support to sponsors to optimize the generation of robust data on the product's benefits and risks and enable accelerated regulatory assessment of new marketing applications. To be eligible for PRIME, a product candidate must meet the eligibility criteria in respect to its potential to offer a major therapeutic advantage over existing treatments, or benefit patients who do not have any treatment options. The benefits of PRIME include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a MAA, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. We may apply for PRIME and it may not be granted. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

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

Regulatory authorities in some jurisdictions, including the U.S. and the EU, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the U.S., or a patient population greater than 200,000 in the U.S. where there is no reasonable expectation that the cost of researching and developing the drug will be recovered from sales in the U.S. Our target indications may include diseases with large patient populations or may include orphan indications. However, there can be no assurances that we will be able to obtain orphan designations for our product candidates.

In the U.S., 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. In addition, if a product candidate that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product candidate is entitled to orphan drug exclusivity. Orphan drug exclusivity in the U.S. provides that the FDA may not approve any other applications, including a full NDA, to market the same drug for the same indication for seven years, except in limited circumstances. The applicable exclusivity period is 10 years in Europe. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified.

Even if we obtain orphan drug designation for a product candidate, we may not be able to obtain or maintain orphan drug exclusivity for that product candidate. We may not be the first to obtain marketing approval of any product candidate for which we have obtained orphan drug designation for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the U.S. 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 designation was materially defective or if we are unable to ensure that we will be able to manufacture sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care or the manufacturer of the product with orphan exclusivity is unable to maintain sufficient product quantity. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the product candidate any advantage in the regulatory review or approval process or entitles the product candidate to Priority Review.

The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

Current and future legislation may increase the difficulty and cost for us to obtain reimbursement for our product candidates.

In the U.S. and some foreign jurisdictions, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the PPACA. Since enactment of the PPACA, there have been and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Act in 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Other legislative changes have been adopted since the PPACA was enacted, including

aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031. Further, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

These laws and other healthcare reform measures may result in additional reductions in Medicare and other healthcare funding and otherwise affect the reimbursement we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product is prescribed or used. We expect that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in coverage and payments from private payors. Accordingly, the implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates.

The prices of prescription pharmaceuticals in the U.S. and foreign jurisdictions are the subject of considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed for marketing.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the U.S. To date, there have been several recent U.S. Congressional inquiries, as well as new measures designed to bring more transparency to pharmaceutical pricing and reduce the costs of pharmaceuticals. For example, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a SIP to import certain prescription products from Canada into the U.S. The final rule is currently the subject of ongoing litigation, but at least six states have passed laws allowing for the importation of products from Canada with the intent of developing SIPs for review and approval by the FDA.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription product and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In many countries, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels, our business could be materially harmed.

We are or may become subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, contractual obligations and failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

There are multiple privacy and data security laws that may impact our business activities, in the U.S. and in other countries where we conduct trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, for example, under HIPAA, HHS has issued regulations to protect the privacy and security of protected health information (PHI) used or disclosed by specific covered entities including certain healthcare providers, health

plans and healthcare clearinghouses. We are not currently classified as a covered entity or business associate under HIPAA. Thus, we are not directly subject to HIPAA's requirements or penalties. The healthcare providers, including certain research institutions from which we may obtain patient or subject health information, may be subject to privacy, security, and breach notification requirements under HIPAA. Additionally, any person may be prosecuted under HIPAA's criminal provisions either directly or under aiding-and-abetting or conspiracy principles. Consequently, depending on the facts and circumstances, we could face criminal penalties if we knowingly receive individually identifiable health information from a HIPAA covered entity, business associate or subcontractor that has not satisfied HIPAA's requirements for disclosure of individually identifiable health information. In addition, in the future, we may maintain sensitive personally identifiable information, including health and genetic information, that we receive throughout the clinical trial process, in the course of our research collaborations, and directly from individuals (or their healthcare providers) who may enroll in patient assistance programs if we choose to implement such programs. As such, we may be subject to various state laws regulating the use or disclosure of this information or requiring notification of affected individuals and state regulators in the event of a breach of personal information, which is a broader class of information than the health information protected by HIPAA.

Furthermore, certain health privacy laws, data breach notification laws, consumer protection laws and genetic information laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our collection, use and dissemination of individuals' health information. Individuals from whom we or our collaborators may obtain health information, as well as the healthcare providers who may share this information with us, may have statutory or contractual rights that limit the ability to use and disclose the information. We may be required to expend significant capital and other resources to ensure ongoing compliance with applicable privacy and data security laws. Claims that we have violated individuals' privacy rights 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.

Additionally, the collection and use of personal data, including data concerning health, in the EU is governed by the GDPR, which extends the geographical scope of EU data protection law to non-EU entities under certain conditions and imposes substantial obligations upon companies and new rights for individuals, as discussed below in "*—Processing of personal data is governed by restrictive laws and regulations in the jurisdictions in which we operate."*

The withdrawal of the U.K. from the EU, commonly referred to as "Brexit," may adversely impact our ability to obtain regulatory approvals for our product candidates in the EU, result in restrictions or imposition of taxes and duties for importing our product candidates into the EU, and may require us to incur additional expenses in order to develop, manufacture and commercialize our product candidates in the EU.

Inadequate funding for the FDA, the SEC and other U.S. government agencies or the EMA or comparable foreign regulatory authorities could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA, EMA or comparable foreign regulatory authorities 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 FDA and other regulators 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, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA, EMA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in recent years, including in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA and the SEC, had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and

process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

In 2020 and 2021 a number of companies announced receipt of CRLs due to the FDA's inability to complete required inspections for their applications. As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

If our product candidates are licensed for marketing and receive federal healthcare reimbursement, any relationships we may have with healthcare providers will be subject to applicable healthcare fraud and abuse laws and regulations, which could expose us to criminal and civil penalties and exclusion from participation in government healthcare programs.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any products for which we are able to obtain marketing approval. Any arrangements we have with healthcare providers, third-party payors and customers will subject us to broadly applicable fraud and abuse and other healthcare laws and regulations. The laws and regulations may constrain the business or financial arrangements and relationships through which we conduct clinical research, market, sell and distribute any products for which we obtain marketing approval. These include the following:

- *Anti-Kickback Statute*. The federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), 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, lease or order of a good, facility, item or service for which payment may be made under a federal healthcare program such as Medicare and Medicaid.
- *False Claims Laws.* The federal false claims and civil monetary penalties laws, including the federal civil False Claims Act, impose criminal and civil penalties, including through civil whistleblower or *qui tam* actions against individuals or entities for, among other things, knowingly presenting or causing to be presented false or fraudulent claims for payment by a federal healthcare 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, with potential liability including mandatory treble damages and significant per-claim penalties.
- *HIPAA.* HIPAA imposes criminal and civil liability for, among other things, executing a scheme or making materially false statements in connection with the delivery of or payment for health care benefits, items or services. Additionally, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations on covered entities and their business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf, including mandatory contractual terms and technical safeguards, with respect to maintaining the privacy, security and transmission of individually identifiable health information.
- *Transparency Requirements.* The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to CMS information related

to payments or transfers of value made to physicians, other healthcare providers and teaching hospitals, as well as information regarding ownership and investment interests held by physicians, other healthcare providers and their immediate family members.

- *Analogous State and Foreign Laws.* Analogous state and foreign fraud and abuse laws and regulations, such as state anti-kickback and false claims laws, can apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors and are generally broad and are enforced by many different federal and state agencies as well as through private actions.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. Infringement of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Our failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Efforts to ensure that any business arrangements we have with third parties and our business generally will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm and the curtailment or restructuring of our operations.

Processing of personal data is governed by restrictive laws and regulations in the jurisdictions in which we operate.

We are or may become subject to many cybersecurity, privacy and data protection laws in the U.S. and around the world. In the U.S., we are subject to numerous federal and state laws governing the collection, processing, use, transmission, disclosure, and sale (collectively, Processing) of personal data (which may also be referred to as personal information, personally identifiable information, and/or non-public personal information).

For example, the CCPA went into effect on January 1, 2020, and established a new privacy framework for covered businesses such as ours. Further, in November 2020, California voters passed the CPRA, which further expands the CCPA with additional data privacy compliance requirements that may impact our business, and establishes a regulatory authority dedicated to enforcing those requirements. While certain of our business activities will not be subject to these laws, it remains unclear how various provisions of the CCPA and CPRA will be interpreted and enforced. In addition, other states, including Virginia and Colorado, already have passed similar state privacy laws. Other states will be considering these laws in the future. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products. These laws also may require us to incur additional costs and expenses in an effort to comply before the laws become effective on January 1, 2023. Recent laws such as the Biometric Information Privacy Act in Illinois have also restricted the use of biometric information. Such laws and regulations require us to continuously review our data processing practices and policies, may cause us to incur substantial costs with respect to compliance.

In addition, outside of the U.S., we are subject to foreign rules and regulations. Many countries outside of the U.S. maintain rigorous laws governing the privacy and security of personal information. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals

who are located in the EEA, and the processing of personal data that takes place in the EEA, is subject to the GDPR, which became effective on May 25, 2018. This provision expanded the scope of data protection in the EU to foreign companies who process the personal data of EU residents, imposed a strict data protection compliance regime with stringent penalties for noncompliance and included new rights for data subjects such as the "portability" of personal data. In particular, under the GDPR, fines of up to €20 million, or up to 4% of the annual global revenue of the noncompliant company, whichever is greater, could be imposed for violations of certain of the GDPR's requirements. If we were found to be in breach of the GDPR, the potential penalties we might face could have a material adverse impact on our business, financial condition, results of operations, and cash flows. Compliance with the GDPR requires time and expense and may require us to make changes to our business operations.

While the GDPR applies uniformly across the EU, each EU Member State is permitted to issue nation-specific data protection legislation, which has created inconsistencies on a country-by-country basis. Brexit has created further uncertainty and could result in the application of new data privacy and protection laws and standards to our operations in the U.K., our handling of personal data of users located in the U.K., and transfers of personal data between the EU and the U.K. Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR. While the Data Protection Act of 2018 in the U.K. that "implements" and complements the GDPR has achieved Royal Assent on May 23, 2018, and is now effective in the U.K., it is still unclear whether transfer of data from the EEA to the U.K. will remain lawful under GDPR. The U.K. government has already determined that it considers all EU and EEA Member States to be adequate for the purposes of data protection, ensuring that data flows from the U.K. to the EU/EEA remain unaffected. In addition, a recent decision from the European Commission appears to deem the U.K. as being "essentially adequate" for purposes of data transfer from the EU to the U.K., although this decision may be re-evaluated in the future.

There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. On July 16, 2020, the European Court of Justice invalidated the EU-U.S. Privacy Shield Framework, a mechanism under which personal data could be transferred from the EEA to U.S. entities that had self-certified under the Privacy Shield Framework. The Court also called into question the Standard Contractual Clauses (SCCs), noting adequate safeguards must be met for SCCs to be valid. European regulatory guidance regarding these issues continues to evolve, and EU regulators across the EU Member States have taken different positions regarding continued data transfers to the U.S. In the future, SCCs and other data transfer mechanisms will face additional challenges.

Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products. Such laws may have potentially conflicting requirements or burdensome obligations that would make compliance challenging or expensive. Such changes may also require us to modify our products and features, and may limit our ability to make use of the data that we collect, may require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs and/or changes in business practices and policies.

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 Process data (including personal data), or in some cases, impact our ability to operate in certain jurisdictions. Any actual or alleged failure to comply with U.S. or international laws and regulations relating to privacy, data protection, and data security could result in governmental investigations, proceedings and enforcement actions (which could include civil or criminal penalties), private litigation or adverse publicity, harm to our reputation, 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 Process the information or impose other obligations or restrictions in connection with our Processing of information, and we may otherwise face contractual restrictions applicable to our Processing of 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.

Our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, suppliers and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, consultants, commercial collaborators, principal investigators, CROs, suppliers and vendors may engage or may have engaged in misconduct or other improper activities. Misconduct by these parties could include failures to comply with FDA, EMA or comparable foreign regulatory authority regulations, provide accurate information to the FDA, EMA or comparable foreign regulatory authorities, comply with federal and state health care fraud and abuse laws and regulations, accurately report financial information or data or disclose unauthorized activities to us. In particular, research, sales, marketing and business arrangements in the health care industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Misconduct by these parties could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of conduct and engage contractors that agree to undertake certain measures with respect to their employees, but it is not always possible to identify and deter misconduct by these parties, 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 a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations.

Our business activities may be subject to the U.S. Foreign Corrupt Practices Act (FCPA) and similar anti-bribery and anti-corruption laws of other countries in which we operate, as well as U.S. and certain foreign export controls, trade sanctions, and import laws and regulations. Compliance with these legal requirements could limit our ability to compete in foreign markets and subject us to liability if we violate them.

Our business activities may be subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA generally prohibits companies and their employees and third-party intermediaries from offering, promising, giving or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, hospitals are owned and operated by the government, and doctors and other hospital employees would be considered foreign officials under the FCPA. Recently, the SEC and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents or contractors, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers or our employees, disgorgement, and other sanctions and remedial measures, and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our products in one or more countries and could materially damage our reputation, our brand, our international activities, our ability to attract and retain employees and our business, prospects, operating results and financial condition.

In addition, our products may be subject to U.S. and foreign export controls, trade sanctions and import laws and regulations. Governmental regulation of the import or export of our products, or our failure to obtain any required import or export authorization for our products, when applicable, could harm our international or domestic sales and adversely affect our revenue. Compliance with applicable regulatory requirements regarding the export of our products may create delays in the introduction of our products in international markets or, in some cases, prevent the export of our products to some countries altogether. Furthermore, U.S. export control laws and economic sanctions prohibit the shipment of certain products and services to countries, governments, and persons targeted by U.S. sanctions. If we fail to comply with export and import regulations and such economic sanctions, penalties could be imposed, including fines and/or denial of certain export privileges. Moreover, any new export or import restrictions, new legislation or shifting approaches in the enforcement or scope of existing regulations, or in the countries, persons, or products targeted by such regulations, could result in decreased use of our products by, or in our decreased ability to export our products to, existing or potential customers with international operations. Any decreased use of our products or limitation on our ability to export or sell our products would likely adversely affect our business.

Risks related to employee matters, managing our growth and other risks related to our business

Our success is highly dependent on our ability to attract, hire and retain highly skilled executive officers and employees.

We currently have a small team focused on research and development of small molecule kinase inhibitors. To succeed, we must recruit, hire, retain, manage and motivate qualified clinical, scientific, technical and management personnel, and we face significant competition for experienced personnel. We are highly dependent on the principal members of our management and scientific and medical staff. If we do not succeed in attracting and retaining qualified personnel, particularly at the management level, it could adversely affect our ability to execute our business plan and harm our operating results. In particular, the loss of one or more of our executive officers could be detrimental to us if we cannot recruit suitable replacements in a timely manner. We could in the future have difficulty attracting and retaining experienced personnel and may be required to expend significant financial resources in our employee recruitment and retention efforts.

Many of the other biotechnology companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. They also may provide higher compensation, more diverse opportunities and better prospects for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are unable to continue to attract and retain high-quality personnel, the rate and success at which we can discover, develop and commercialize our product candidates will be limited and the potential for successfully growing our business will be harmed.

Additionally, we rely on our scientific founder and head scientific advisor, physician-scientist partners and other scientific and clinical advisors and consultants to assist us in formulating our research, development and clinical strategies. Most of these advisors and consultants are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us. In addition, these advisors and consultants typically will not enter into non-compete agreements with us. If a conflict of interest arises between their work for us and their work for another entity, we may lose their services. Furthermore, our advisors may have arrangements with other companies to assist those companies in developing products or technologies that may compete with ours. In particular, if we are unable to maintain consulting or employment relationships with our scientific founder and head scientific advisor, physician-scientist partners and other scientific and clinical advisors, or if they provide services to our competitors, our development and commercialization efforts will be impaired and our business will be significantly harmed. For example, if we are no longer able to access our network of physician-scientists, our ability to define and characterize patients' needs for future product candidate development may be negatively affected.

Our reliance on a limited number of employees who provide various administrative, research and development, and other services across our organization presents operational challenges that may adversely affect our business.

As of December 31, 2021, we had 40 full-time employees, upon which we rely for various administrative, research and development, and other support services. The small size of our centralized team may limit our ability to devote adequate personnel, time, and resources to support our operations or research and development activities, and the management of financial, accounting, and reporting matters. If our team fails to provide adequate administrative, research and development, or other services across our organization, our business, financial condition, and results of operations could be harmed.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

As of December 31, 2021, we had 40 full-time employees, including 29 employees engaged in research and development activities. In order to successfully implement our development and commercialization plans and strategies, and as we transition into operating as a public company, we expect to need significant additional managerial, operational, sales, marketing, financial and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining, retaining and motivating our current and additional employees;
- managing our internal development efforts effectively, including the preclinical, clinical, FDA, EMA and other comparable foreign regulatory authorities' review process for NVL-520 and NVL-655 and our other programs, while complying with any contractual obligations to contractors and other third parties;
- managing increasing operational and managerial complexity; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to successfully develop and, if approved, commercialize NVL-520, NVL-655 and any future product candidates developed from our ALK IXDN, HER2 and other discovery programs and other product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services, including key aspects of research, clinical development and manufacturing. There can be no assurance that the services of independent 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 third-party service providers is compromised for any reason, our preclinical studies and clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval for any of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing third-party service providers or find other competent outside contractors and consultants on economically reasonable terms, or at all.

If we are not able to effectively expand our organization by hiring new employees and/or engaging additional third-party service providers, we may not be able to successfully implement the tasks necessary to further develop and commercialize NVL-520, NVL- 655, or any future product candidate from our programs and any of our other product candidates and, accordingly, may not achieve our research, development and commercialization goals.

Our internal computer systems, or those of any of our CROs, manufacturers, other contractors or consultants or potential future collaborators, may fail or suffer actual or suspected security or data privacy breaches or other unauthorized or improper access to, use of, or destruction of our proprietary or confidential data,

employee data, or personal data, which could result in additional costs, loss of revenue, significant liabilities, harm to our brand and material disruption of our operations, and potentially significant delays in our delivery to market.

Despite the implementation of security measures in an effort to protect systems that store our data, given their size and complexity and the increasing amounts of information maintained on our internal information technology systems and external processing and storage systems (i.e., cloud), and those of our third-party CROs, other contractors (including sites performing our clinical trials) and consultants, these systems are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners, and/or other third parties, 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), which may compromise our system infrastructure or lead to the loss, destruction, alteration or dissemination of, or damage to, our data. For example, companies have experienced an increase in phishing and social engineering attacks from third parties in connection with the COVID-19 pandemic. Also, while we have opened our office for use under strict guidelines as required by federal, state, and local authorities, a majority of our employees are working remotely. As a result, we may have increased cyber security and data security risks, due to increased use of home wi-fi networks and virtual private networks, as well as increased disbursement of physical machines. While we implement IT controls to reduce the risk of a cyber security or data security breach, there is no guarantee that these measures will be adequate to safeguard all systems.

To the extent that any disruption or security breach were to result in a loss, destruction, unavailability, alteration or dissemination of, or damage to, our data (including confidential information and personal data) or applications, or for it to be believed or reported that any of these occurred, we could incur liability and reputational damage and the development and commercialization of our product candidates could be delayed. There can be no assurance that our data protection efforts and our investment in information technology, or the efforts or investments of CROs, consultants or other third parties, will prevent significant breakdowns or breaches in systems or other cyber incidents that cause loss, destruction, unavailability, alteration or dissemination of, or damage to, our data that could have a material adverse effect upon our reputation, business, operations or financial condition. For example, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs and the development of our product candidates could be delayed. In addition, the loss of clinical trial data for our product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data, as well as claims or investigations from regulators or other third parties. Furthermore, significant disruptions of our internal information technology systems or security breaches could result in the loss, misappropriation, and/or unauthorized access, use, or disclosure of, or the prevention of access to, data (including trade secrets or other confidential information, intellectual property, proprietary business information, and personal data), which could result in financial, legal, business, and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal data, including personal data 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 financial exposure related to investigation of the incident (including cost of forensic examinations), subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of data, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business.

Notifications, follow-up actions, claims and investigations related to a security incident could impact our reputation and cause us to incur significant costs, including legal expenses and remediation costs. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the lost data. We expect to incur significant costs in an effort to detect and prevent security incidents, and we may face increased costs and

requirements to expend substantial resources in the event of an actual or perceived security breach. We also rely on third parties to manufacture our product candidates, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security incident were to result in a loss, destruction or alteration of, or damage to, our data (including personal data), or inappropriate disclosure of confidential or proprietary information, we could be exposed to litigation and governmental investigations, the further development and commercialization of our product candidates could be delayed, and we could be subject to significant fines or penalties for any noncompliance with certain state, federal and/or privacy and security laws from countries outside of the U.S.

Our insurance policies may not be adequate to compensate us for the potential losses arising from any such disruption in or, failure or security breach of our systems or third-party systems where information important to our business operations or commercial development is stored. In addition, such insurance may not be available to us in the future on economically reasonable terms, or at all. Further, our insurance may not cover all claims made against us and could have high deductibles in any event, and defending a suit, regardless of its merit, could be costly and divert management attention.

Many of our research, manufacturing and preclinical activities are conducted by third parties outside of the U.S., including without limitation in China and India. A significant disruption in the operations of those third parties, a war, a trade war or political unrest could materially adversely affect our business, financial condition and results of operations.

We contract many of our research, manufacturing and preclinical activities to third parties outside the U.S., including without limitation in China and India. Any disruption in the operations of such third parties or in their ability to meet our needs, whether as a result of a natural disaster, war or other causes, could impair our ability to operate our business on a day-to-day basis and to continue development of our programs. Furthermore, since many of these third parties are located outside the U.S., we are exposed to the possibility of disruption and increased costs in the event of changes in the policies of the U.S. or foreign governments, war, political unrest or unstable economic conditions in any of the countries where we conduct such activities. For example, a war or trade war could lead to tariffs, embargoes, sanctions or other limitations on trade, including without limitation those placed on Russia as a result of its military invasion of Ukraine, that may affect our ability to source the chemical intermediates used in our product candidates. By way of further example, a natural disaster, war, civil or political unrest or similar circumstances could hinder our ability to maintain or initiate clinical studies at our preferred sites, causing trial initiation or implementation delays. Any of these matters could materially and adversely affect our development timelines, business and financial condition.

Our operations are vulnerable to interruption by flood, fire, earthquakes, power loss, telecommunications failure, terrorist activity, pandemics and other events beyond our control, which could harm our business.

Our corporate headquarters are located in Cambridge, Massachusetts. We have not undertaken a systematic analysis of the potential consequences to our business and financial results from a major flood, fire, earthquake, power loss, telecommunications failure, terrorist activity, pandemics or other disasters and do not have a recovery plan for such disasters. In addition, we do not carry sufficient insurance to compensate us for actual losses from interruption of our business that may occur, and any losses or damages incurred by us could harm our business. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

If we are unable to establish sales or marketing capabilities or enter into agreements with third parties to sell or market our product candidates, we may not be able to successfully sell or market our product candidates that obtain regulatory approval.

We currently do not have and have never had a marketing or sales team. In order to commercialize any product candidates, if approved, we must build marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services for each of the territories in which we may have approval to sell or market our product candidates. We may not be successful in accomplishing these required tasks.

Establishing an internal sales or marketing team with technical expertise and supporting distribution capabilities to commercialize our product candidates will be expensive and time-consuming and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities could adversely impact the commercialization of any of our product candidates that we obtain approval to market if we do not have arrangements in place with third parties to provide such services on our behalf. Alternatively, if we choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems, we will be required to negotiate and enter into arrangements with such third parties relating to the proposed collaboration and such arrangements may prove to be less profitable than commercializing the product on our own. If we are unable to enter into such arrangements when needed, on acceptable terms or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval, or any such commercialization may experience delays or limitations. If we are unable to successfully commercialize our approved product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer, and we may incur significant additional losses.

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

We may seek regulatory approval of our product candidates outside of the U.S. and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements and reimbursement regimes in foreign countries, such as the lack of pathways for accelerated drug approval, may result in foreign regulatory approvals taking longer and being more costly than obtaining approval in the U.S.;
- foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials or our interpretation of data from preclinical studies or clinical trials;
- approval policies or regulations of foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval;
- impact of the COVID-19 pandemic on our ability to produce our product candidates and conduct clinical trials in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with legal requirements applicable to privacy, data protection, information security and other matters;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes and government payors in foreign countries;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- potential liability under the FCPA or comparable foreign regulations;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the U.S.;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, trade policies, treaties and tariffs.

These and other risks associated with international operations may materially adversely affect our ability to attain or maintain profitable operations.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service, the U.S. Treasury Department and other applicable tax authorities. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

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

Our federal net operating loss (NOL) carryforwards may be unavailable to offset future taxable income because of restrictions under U.S. tax law. Under tax legislation commonly referred to as the Tax Act as amended by the Coronavirus Aid, Relief, and Economic Security Act, our federal NOLs may be carried forward indefinitely, but for taxable years beginning after December 31, 2020, the deductibility of federal NOL carryforwards generated in tax years beginning after December 31, 2017 is limited to 80% of our current year taxable income. It is uncertain if and to what extent various states will conform to the Tax Act. As of December 31, 2021, we had available federal NOL carryforwards of approximately $73.2 million and available state NOL carryforwards of approximately $72.5 million, which begin to expire in 2037.

In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), if a corporation undergoes an “ownership change” (generally defined as a cumulative change in the corporation’s ownership by “5-percent shareholders” that exceeds 50 percentage points (by value) over a rolling three-year period), the corporation’s ability to use its pre-change NOL carryforwards and certain other pre-change tax attributes to offset its post-change taxable income may be limited. Similar rules may apply under state tax laws. We may have experienced such ownership changes in the past, and we may experience ownership changes in the future as a result of shifts in our stock ownership, some of which are outside our control. We have not conducted any studies to determine annual limitations, if any, that could result from such changes in the ownership. There is also a risk that due to regulatory changes, such as suspensions on the use of NOL carryforwards, or other unforeseen reasons, our existing NOL carryforwards could expire or otherwise be unavailable to offset future income tax liabilities. Because our ability to utilize our NOL carryforwards and certain other tax attributes could be limited as described above, we may not be able to utilize a material portion of our NOL carryforwards and certain other tax attributes, which could have a material adverse effect on our cash flows and results of operations.

Risks related to our intellectual property

Derivation proceedings may be necessary to determine priority of inventions, and an unfavorable outcome may require us to cease using the related technology or to attempt to license rights from the prevailing party.

Derivation proceedings provoked by third parties or brought by us or declared by the U.S. Patent and Trademark Office (USPTO) may be necessary to determine the priority of inventions with respect to one or more of our patents or patent applications or those of our future licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be adversely affected if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with such proceedings could have a

material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our development programs, license necessary technology from third parties or enter into development or manufacturing partnerships that would help us bring our product candidates to market.

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

Our success depends in large part on our ability to obtain and maintain protection of the intellectual property rights we own (either solely and jointly with others), or may in the future license from third parties (in particular, worldwide patents relating to any proprietary technology and product candidates we develop). To date, we have not yet obtained or exclusively in-licensed any issued patents, and all of the patent applications that we own are at a very early stage of prosecution. Accordingly, unless and until any of our patent applications issue or we otherwise acquire rights in any issued patents, we must rely on trade secret protection and other intellectual property rights to prevent use of our inventions by others and protect our proprietary rights We also seek to protect our proprietary position by filing patent applications in the U.S. and select other countries related to our technologies and product candidates that are important to our business and by in-licensing intellectual property related to such technologies and product candidates. However, we cannot guarantee that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications we may file in the future, nor can we be sure that any patents that may be granted to us in the future will be commercially useful in protecting our products, or the methods of use or manufacture of those products. If we are unable to obtain and maintain meaningful patent protection in jurisdictions important to our business for our product candidates, their respective components, formulations, combination therapies, methods used to manufacture them and methods of treatment, or other proprietary technologies our business, financial condition, results of operations and prospects could be adversely affected.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain or defend all necessary or desirable patent applications at a reasonable cost or in a timely manner. 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, in some circumstances involving technology that we may license from third parties, we may not have the sole right to control the preparation, filing and prosecution of patent applications or to maintain, enforce and defend the in-licensed patents. Therefore, any in-licensed patents and applications may not be prepared, filed, prosecuted, maintained, defended and enforced in a manner consistent with the best interests of our business.

The patent rights of pharmaceutical and biotechnology companies, like ours, generally are highly uncertain, involve complex legal and factual questions and have been the subject of much litigation in recent years. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents, particularly those related to oncology, has emerged in the U.S. The relevant patent laws and their interpretation outside of the U.S. are also uncertain. Various courts, including the U.S. Supreme Court, have rendered decisions that affect the scope of patent eligibility of certain inventions or discoveries relating to biotechnology. These decisions conclude, among other things, that abstract ideas, natural phenomena and laws of nature are not themselves patent eligible subject matter. Precisely what constitutes a law of nature or abstract idea is uncertain, and certain aspects of our technology could be considered ineligible for patenting under applicable law. In addition, the scope of patent protection outside the U.S. is uncertain, and laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. or vice versa. For example, European patent law precludes the patentability of methods of treatment of the human body. We cannot predict whether the patent applications we are currently pursuing will issue as patents that protect our technology and product candidates, in whole or in part, in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors. Changes in either the patent laws or interpretation of the patent laws in the U.S. or other countries may diminish the value of our patents and our ability to obtain, protect, maintain, defend and enforce our patent rights, narrow the scope of our patent protection and, more generally, affect the value or narrow the scope of our patent rights.

Further, third parties may have intellectual property rights relating to our product candidates of which we are unaware. For example, third parties may have blocking patents that could be used to prevent us from commercializing our product candidates and practicing our proprietary technology. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing, or in some cases are not published at all. Therefore, neither we nor our future licensors can know with certainty whether either we or our future licensors were the first to make the inventions claimed in the patent applications we own or any patents or patent applications we may own or in-license in the future, or that either we or any of our future licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our owned and future in-licensed patent rights are uncertain. For example, currently unpublished patent applications may later publish and limit our ability to obtain valid and enforceable patents.

Moreover, any issued patents we do obtain or in-license may be challenged, invalidated, or circumvented. We or our future licensors may be subject to a third-party pre-issuance submission of prior art to the USPTO, or to a foreign patent office, or become involved in opposition, derivation, revocation, reexamination, *inter partes* review, post-grant review or interference proceedings 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 product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize drugs without infringing third-party patent rights. If the breadth or strength of protection provided by any patents we obtain and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Moreover, our competitors may independently develop similar technologies that are outside the scope of the rights granted under any issued patents we may obtain. For these reasons and others, we may face competition with respect to our product candidates.

Additionally, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if our owned and any future in-licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us, or otherwise provide us with any competitive advantage. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and any patents we do obtain may be challenged in the courts or patent offices in the U.S. and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in 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 product candidates. Such challenges also may result in substantial cost and require significant time from our management and employees, even if the eventual outcome is favorable to us. Furthermore, our competitors may be able to circumvent any patents we obtain or in-license in the future by developing similar or alternative technologies or products in a non-infringing manner. For these reasons, even if we are successful in obtaining patents or in-licensing patents in the future, our patent portfolio may not provide us with sufficient rights to exclude others from using or commercializing technology and products similar or identical to any of our technology and product candidates for any period of time.

Patent terms may not protect our competitive position for an adequate amount of time.

Issued patents can provide protection for varying periods of time, depending, for example, upon the type of patent, the date of filing of the patent application, the date of patent issuance and the legal term of patents in the countries in which they are obtained. However, patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. The term of a patent outside of the U.S. varies in accordance with the laws of the foreign jurisdiction. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics. 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 approved for use or commercialized.

If we do not obtain patent term extension in the U.S. under the Hatch-Waxman Act and in foreign countries under similar legislation, which if granted could extend the term of our marketing exclusivity for any product candidates we may develop, our business may be materially and adversely affected.

In the U.S., the term of a patent that covers an FDA-approved drug may be eligible for limited patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. In addition, the patent term of only one patent applicable to an approved drug may be extended, and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. Similar provisions are available in Europe and certain other non-U.S. jurisdictions to extend the term of a patent that covers an approved drug. While, in the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on any patents that issue covering those product candidates, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted and, even if granted, the length of such extensions. We may not be granted patent term extension either in the U.S. or in any foreign country, even where we obtain a patent that is eligible for patent term extension, if, for example, an applicable government authority determines that we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. If we obtain such an extension, it may be for a shorter period than we had sought. If we are unable to obtain any patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following the expiration of our patent rights, and our business, financial condition, results of operations and prospects could be materially and adversely affected.

Furthermore, for any patents we may in-license in the future, we may not have the right to control prosecution, including filing with the USPTO, of a petition for patent term extension under the Hatch-Waxman Act. Thus, if a patent we in-license in the future is eligible for patent term extension under the Hatch-Waxman Act, we may not be able to control whether a petition to obtain a patent term extension is filed or whether the requested extension is obtained from the USPTO.

Also, there are detailed rules and requirements regarding the patents that may be submitted to the FDA for listing in the Approved Drug Products with Therapeutic Equivalence Evaluations, or the Orange Book. We may be unable to obtain or in-license patents covering our product candidates that contain one or more claims that satisfy the requirements for listing in the Orange Book. Even if we or our future licensors submit a patent for listing in the Orange Book, the FDA may decline to list the patent, or a manufacturer of generic drugs may challenge the listing. If one of our product candidates is approved and a patent covering that product candidate is not listed in the Orange Book, a manufacturer of generic drugs would not have to provide advance notice to us of any abbreviated new drug application filed with the FDA to obtain permission to sell a generic version of such product candidate.

Changes to patent laws in the U.S. and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of patent laws in the U.S. or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of our owned and any future in-licensed patent applications and the maintenance, enforcement or defense of any issued patents we may obtain or in-license.

In addition, the patent positions of companies in the development and commercialization of pharmaceuticals are particularly uncertain. For example, the USPTO regularly revises its policies and procedures for patent examination. Future political changes may impose new difficulties in obtaining patent protection. This combination of events has increased uncertainty with respect to the validity and enforceability of patents once

obtained. Similarly, foreign courts and patent offices have made, and will likely continue to make, changes in how the patent laws in their respective jurisdictions are interpreted. We cannot predict future changes in the interpretation of patent laws or changes to patent laws that might be enacted into law by U.S. and foreign legislative bodies. Those changes may materially affect our patents or patent applications and our ability to obtain patent protection in the future.

We may become involved in lawsuits to protect or enforce our patent or other intellectual property rights, which could be expensive, time-consuming and unsuccessful.

Competitors and other third parties may infringe, misappropriate or otherwise violate patents or other intellectual property that we own or license. As a result, we or our future licensors may need to file infringement, misappropriation or other intellectual property claims, which can be expensive and time-consuming. Any claims we assert against others could provoke them to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property rights. Our ability to stop third parties from making, using, selling, offering to sell, or importing products that infringe our intellectual property will depend in part on in the extent to which we obtain and enforce patent claims that cover our technology, inventions, and improvements.

Furthermore, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability. In a patent infringement proceeding, the perceived infringers could counterclaim that the patents we or our licensors have asserted are invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity or unenforceability are common. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may institute such claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings and equivalent proceedings in foreign jurisdictions, such as opposition proceedings in the European Patent Office. The outcomes of allegations of invalidity or unenforceability are unpredictable. With respect to validity, for example, even if we are successful in obtaining patents or in-licensing patents, we cannot be certain that there is no invalidating prior art of which the patent examiner and we or our future licensing partners were unaware during prosecution.

An adverse result in any such proceeding could put one or more of the patents that we may own or in-license in the future at risk of being invalidated or interpreted narrowly, and could put any of our present or future owned or in-licensed patent applications at risk of not yielding an issued patent. A court may also refuse to stop the third party from using the technology at issue in a proceeding, for example, on the basis that our owned or in-licensed patents do not cover that technology. Furthermore, if the breadth or strength of protection provided by our patent applications and any future patents is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future products, diagnostic tests or services.

In addition, interference or derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patent applications or any future patents. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be adversely affected if the prevailing party does not offer us a license on commercially reasonable terms or at all, or if a non-exclusive license is offered and our competitors gain access to the same technology. Our defense of litigation or interference or derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our discovery programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market.

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 or trade secrets could be compromised by

disclosure during litigation. Any of the foregoing could allow third parties to develop and commercialize competing technologies and products and have a material adverse impact on our business, financial condition, results of operations and prospects.

Third parties may allege that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. There is considerable patent and other intellectual property litigation in the pharmaceutical and biotechnology industries. We may become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and product candidates, including interference proceedings, post grant review, *inter partes* review and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, including our competitors, exist in the fields in which we are pursuing product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our technologies or product candidates may be subject to claims that they infringe the patent rights of third parties. Our competitors and others may have significantly larger and more mature patent portfolios than we have. In addition, future litigation may be initiated by patent holding companies or other third parties who have no relevant product or service revenue and against whom our future patents, if any, may provide little or no deterrence or protection. Competitors may also assert that our product candidates infringe their intellectual property rights as part of a business strategy to impede our successful entry into those markets.

The legal threshold for initiating litigation or contested proceedings is low, so that even lawsuits or proceedings with a low probability of success might be initiated and require significant resources and management attention to defend. The risks of being involved in such litigation and proceedings may increase if and as our product candidates near commercialization and as we gain greater visibility as a public company. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of merit. Because patent applications can take many years to issue, pending patent applications may result in issued patents that our product candidates infringe. For example, there may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the discovery, use or manufacture of our product candidates or technologies. We may not be aware of all such intellectual property rights potentially relating to our technology and product candidates, or we may incorrectly conclude that third-party intellectual property is invalid or that our activities and product candidates do not infringe the intellectual property rights of third parties. Thus, we do not know with certainty that our technology and product candidates, or our development and commercialization thereof, do not and will not infringe, misappropriate or otherwise violate any third party's intellectual property rights. Parties making claims against us may also obtain injunctive or other equitable relief. For example, if any third-party patents were held to cover the manufacturing process of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidates. In the event of a successful claim of infringement against us, we may also have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, indemnify customers, collaborators or other third parties, seek new regulatory approvals, and redesign our infringing products, which may not be possible or practical. If we are found to infringe, misappropriate or otherwise violate a third party's intellectual property rights, we may be required to obtain a license from such third party to continue developing, manufacturing and marketing our technology and 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 a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and could require us to make substantial licensing and royalty payments. Claims that we have misappropriated the confidential information, trade secrets or other intellectual property rights of third parties could have a similar material adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to obtain licenses from third parties on commercially reasonable terms, our business could be adversely affected.

It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from the third parties. The in-licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to in-license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. Furthermore, companies that perceive us to be a competitor may be unwilling to sell, assign or license rights to us. In addition, we expect that competition for the in-licensing or acquisition of third-party intellectual property rights for product candidates that are attractive to us may increase in the future, which may mean fewer suitable opportunities for us as well as higher acquisition or licensing costs. If we are unable to license such technology, or if we are forced to license such technology on unfavorable terms, such as substantial licensing or royalty payments, our business could be materially and adversely affected. If we are unable to obtain a necessary license, the third parties owning such intellectual property rights could seek an injunction prohibiting our sales or we may be unable to otherwise develop or commercialize the affected product candidates, which could materially harm our business. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

If we are unable to obtain rights to required third-party intellectual property rights, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology and product candidates, which could harm our business, financial condition, results of operations, and prospects significantly.

If we fail to comply with our obligations in any future intellectual property licenses with third parties that we may enter into, or otherwise experience disruptions to our business relationships with our future licensors, we could lose intellectual property rights that are important to our business.

We may in the future enter into licensing and funding arrangements with third parties that may impose, among other things, diligence, development, and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with those obligations, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market, or may be forced to cease developing, manufacturing or marketing, any product that is covered by these agreements or may face other penalties under such agreements, or our counterparties may require us to grant them certain rights. Such an occurrence could materially adversely affect the value of any product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements, or restrictions on our ability to freely assign or sublicense our rights under such agreements when it is in the interest of our business to do so, may result in our having to negotiate new or reinstated agreements with less favorable terms, cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, which would have a material adverse effect on our business, financial condition, results of operations, and prospects, or impede, delay or prohibit the further development or commercialization of, one or more product candidates that rely on such agreements.

For example, disputes may arise regarding intellectual property that is or becomes subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other matters of contract interpretation;
- whether and the extent to which our technology and processes infringe the intellectual property rights of the licensor that are not subject to the licensing agreement;
- whether our licensor or its licensor had the right to grant the license agreement;

- whether third parties are entitled to compensation or equitable relief, such as an injunction, for our use of the intellectual property rights without their authorization;
- our involvement in the prosecution of licensed patents and our licensors' overall patent enforcement strategy;
- the amounts of royalties, milestones or other payments due under the license agreement;
- the sublicensing of patent and other rights under collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.
- If we do not prevail in such disputes, we may lose any or all of our rights under such license agreements.

In addition, intellectual property license agreements are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we may license prevent or impair our ability to maintain our licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected technology and product candidates, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our future licensors may rely on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents and patent applications we may in-license. If other third parties have ownership rights to patents and/or patent applications we may in-license, they may be able to license such patents to 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 in-licensed patents in order to enforce such patents against third parties, and we may not receive such cooperation. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

Despite our efforts, our future licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize product candidates and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, competitors could seek regulatory approval for and market products and technologies identical to ours. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

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

Third parties may attempt to develop and commercialize competitive products in foreign countries where we do not have any patent protection and/or where legal recourse may be limited. This may have a significant commercial impact on our foreign business operations.

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S., and even where such protection is nominally available, adequate judicial and governmental enforcement of such intellectual property rights may be lacking. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling our inventions in such countries or importing products made using our inventions into the U.S. or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to

territories where we do obtain patent protection or future licenses but enforcement is not as strong as that in the U.S. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop the infringement of any patents we do obtain or in-license or marketing of competing products in violation of our intellectual property and proprietary rights generally. In addition, certain jurisdictions do not protect, to the same extent as the U.S. or at all, inventions that constitute new methods of treatment.

Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put any patents we obtain 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. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We work with third-party contractors located in China to develop certain of our intellectual property. On December 1, 2020, the Chinese government implemented a new Export Control Law which regulates the export of certain technologies outside of China. As currently implemented, we do not believe the Export Control Law applies to our product candidates, and we do not expect it to impact our business; however the Export Control Law could be amended in the future in a way that could adversely affect our business.

Many countries, including India, China and certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. 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 patents. If we do obtain or in-license patents and we or any of our licensors 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.

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

We or our future licensors may be subject to claims that current or former employees, collaborators, CROs, universities or other third parties have an interest in our owned or future in-licensed patents and patent applications, trade secrets or other intellectual property as an inventor, co-inventor, owner or co-owner. For example, we or our future licensors may have inventorship or ownership disputes arise from conflicting obligations of employees, consultants, CROs or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership of any future owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, we may be required to pay monetary damages and we may also lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Additionally, if residents of other countries can claim inventorship of our patents and patent applications, we may be required to fulfill additional obligations. For example, some countries, including China, require a patent owner to provide remuneration to inventors who assign rights to inventions developed during course of their employment. Litigation may be necessary to defend against claims based on foreign inventors. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

Intellectual property discovered through government funded programs may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

We may in the future develop, acquire, or license intellectual property rights that have been generated through the use of U.S. government funding or grants. Pursuant to the Bayh-Dole Act of 1980, the U.S. government has certain rights in inventions developed with government funding. These U.S. government rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (1) adequate steps have not been taken to commercialize the invention; (2) government action is necessary to meet public health or safety needs; or (3) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). If the U.S. government exercises its "march-in" rights in any future intellectual property rights that are generated through the use of U.S. government funding or grants, we could be forced to license or sublicense intellectual property developed by us or that we may license on terms unfavorable to us, and there can be no assurance that we would receive compensation from the U.S. government for the exercise of such rights. The U.S. government also has the right to take title to these inventions if the grant recipient fails to disclose the invention to the government or fails to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U.S. government requires that any products embodying any of these inventions or produced through the use of any of these inventions be manufactured substantially in the U.S. This preference for U.S. industry may be waived by the federal agency that provided the funding if the owner or assignee of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the U.S. or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. industry may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. Any exercise by the government of any of the foregoing rights could harm our competitive position, business, financial condition, results of operations and prospects.

We may be subject to claims by third parties asserting that our employees, consultants or contractors have wrongfully used or disclosed confidential information of such third parties, or that they have wrongfully used or disclosed alleged trade secrets of their current or former employers, or that we have misappropriated their intellectual property, or that they own what we regard as our own intellectual property.

Many of our employees, physician-scientist partners, consultants and contractors are or were previously employed at or engaged by universities or other pharmaceutical or biotechnology companies, including our competitors or potential competitors. Many of them executed proprietary rights, non-disclosure and/or non-competition agreements in connection with such previous employment or engagement. Although we try to ensure that the individuals who work for us do not use the intellectual property rights, proprietary information, know-how or trade secrets of others in their work for us, we may be subject to claims that we or they have, inadvertently or otherwise, used, infringed, misappropriated or otherwise violated the intellectual property rights, or disclosed the alleged trade secrets or other proprietary information, of these former employers, competitors or other third parties. We may also be subject to claims that we have improperly used or obtained such trade secrets. Litigation may be necessary to defend against these claims. Any litigation or the threat of litigation may adversely affect our ability to hire employees or engage consultants and contractors. A loss of key personnel or their work product could hamper or prevent us from developing and commercializing products and product candidates, which could harm our business.

In addition, while it is our policy to require our employees, physician-scientist partners, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in obtaining such an agreement from each party who in fact develops intellectual property that we regard as our own. Our intellectual property assignment agreements

with them may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. Additionally, assignment agreements and related agreements may be interpreted under the laws of a foreign country, which may be unpredictable. Such claims could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If we fail in prosecuting or defending any such claims, we may be required to pay monetary damages, and we may also lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive position and prospects. Such intellectual property rights 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, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and employees.

If we are unable to protect the confidentiality of our trade secrets and other proprietary information, our business and competitive position would be adversely affected.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology and other proprietary information to maintain our competitive position. We seek to protect our trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, our unpublished patent applications or other confidential research, and we may not be able to obtain adequate remedies for such breaches. Detecting the disclosure or misappropriation of a trade secret and 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 inside and outside the U.S. 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 them, or those to whom they communicate such trade secrets, from using that technology or information to compete with us.

Furthermore, we expect that, over time, our trade secrets, know-how and proprietary information may be disseminated within the industry through independent development, the publication of journal articles and the movement of personnel to and from academic and industry scientific positions. Consequently, without costly efforts to protect our proprietary technology, we may be unable to prevent others from exploiting that technology, which could affect our ability to expand in domestic and international markets. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely affected.

We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. These security measures may be breached or otherwise accessed in an unauthorized manner, and we may not have adequate remedies for any breach.

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

If our trademarks and trade names are not adequately protected, we may not be able to build name recognition in our markets of interest and our business may be adversely affected. Our trademarks or trade names may be challenged, infringed, circumvented, declared generic or determined to be infringing on other marks. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition or cancellation proceedings. This can be time-consuming and expensive, particularly for a company of our size. In addition, in an infringement proceeding, a court may decide

that a trademark of ours is not valid or is unenforceable, or may determine another trademark is not infringing our trademarks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these trademarks or trade names, which we need to build name recognition among potential collaborators or customers in our markets of interest. At times, competitors may adopt trademarks or trade names similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trademark or trade name infringement claims brought by owners of other registered trademarks or trade names that incorporate variations of our trademarks or trade names. Over the long term, if we are unable to successfully register our trademarks and trade names and establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks and trade names may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

Our current trademark applications and additional trademark applications we may file in the future may not proceed to registration and/or may be opposed by third parties. Even if such applications proceed to registration, third parties may challenge our use of such trademarks or seek to invalidate our registration in the future. Other companies in our industry may be using trademarks that are similar to ours and may in the future allege that the use of our trademarks in connection with our products infringes or otherwise violates their trademark rights. Trademark-granting authorities may decide to investigate our trademarks on their own initiative if they believe that there may be potential issues to be resolved. In addition, failure to maintain our trademark registrations, or to obtain new trademark registrations in the future, could limit our ability to protect and enforce our trademarks and impede our marketing efforts in the countries in which we operate. Over the long term, if we are unable to establish brand recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected.

Risks related to our dependence on third parties

We rely on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research and studies.

We utilize and depend upon independent investigators and collaborators, such as medical institutions, CROs, CMOs, and strategic partners (collectively, partners) to conduct and support our preclinical studies and our clinical trials under agreements with us and plan to continue to do so for our future clinical trials. These third parties have had and will continue to have a significant role in the conduct of our preclinical studies and clinical trials and the subsequent collection and analysis of data. For example, our partners contribute highly enabling technologies and services that include: (i) numerous physician-scientists at leading CROs, (ii) support for our translational research efforts, (iii) crystallography to enable structure-based drug discovery, (iv) biochemical and cell-based assays to guide lead generation and optimization, and (v) patient-derived, cell and xenograft models to translate our findings to the clinical setting.

These third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we have limited ability to control the amount or timing of resources that any such third party will devote to our preclinical studies or our clinical trials. The third parties we rely on for these services 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 drug development activities, which could affect their performance on our behalf. Some of these third parties may terminate their engagements with us at any time. We also expect to have to negotiate budgets and contracts with CROs, clinical trial sites and CMOs and we may not be able to do so on favorable terms, which may result in delays to our development timelines and increased costs. If we need to enter into alternative arrangements with, or replace or add any third parties, it would involve substantial cost and require extensive management time and focus, or involve a transition period, and may delay our drug development activities, as well as materially impact our ability to meet our desired clinical development timelines.

Our heavy reliance on these third parties for such drug development activities will reduce our control over these activities. As a result, we will have less direct control over the conduct, timing and completion of preclinical studies and clinical trials and the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Nevertheless, we are responsible for ensuring that each of our studies and trials is conducted in accordance with applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCP standards, regulations for conducting, recording and reporting the results of clinical trials to assure that data and reported results are reliable and accurate and that the rights, integrity and confidentiality of trial participants are protected. The EMA also requires us to comply with similar standards. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. There can be no assurance that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials substantially comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under current cGMP regulations and will require a large number of test patients. Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients, may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

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, or if these third parties need to be replaced, 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 product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We contract with third parties for the manufacture of our product candidates for preclinical studies and clinical trials, and expect to continue to do so for additional preclinical studies, clinical trials and ultimately for commercialization. This reliance on third parties increases the risk that we will not have sufficient quality and quantities of our product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not currently have the infrastructure or internal capability to manufacture supplies of our product candidates for use in development and commercialization. We rely, and expect to continue to rely, on third-party manufacturers for the production of our product candidates for preclinical studies and clinical trials under the guidance of members of our organization. We do not have long-term supply agreements, and we enter into contracts for the production of our product candidates on an as-needed basis, which means that aside from any binding purchase orders we have from time to time, we are subject to the supplier's plant availability, ability to manufacture on our behalf, and/or a change the terms on which it is willing to continue supplying to us at any time. If we were to experience an unexpected loss of supply of any of our product candidates for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing preclinical studies or clinical trials.

We expect to continue to rely on third-party manufacturers for the commercial supply of any of our product candidates for which we obtain marketing approval. We may be unable to maintain or establish required agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the failure of the third party to manufacture our product candidates according to our schedule and specifications, or at all, including if our third-party contractors give greater priority to the supply of other

products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreements between us and them;

- the reduction or termination of production or deliveries by suppliers, or the raising or prices or renegotiation of terms;
- the termination or nonrenewal of arrangements or agreements by our third-party contractors at a time that is costly or inconvenient for us;
- the breach by the third-party contractors of our agreements with them;
- the failure of the third party to manufacture our product candidates according to our specifications;
- the failure of third-party contractors to comply with applicable regulatory requirements, including cGMPs;
- the mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified;
- clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales; and
- the misappropriation of our proprietary information, including our trade secrets and know-how.

We do not have complete control over all aspects of the manufacturing process of our contract manufacturing partners and are dependent on these contract manufacturing partners for general project management, in-person oversight and for compliance with cGMP regulations for manufacturing both API and finished drug products. To date, we have obtained API and drug product for our product candidates from single-source third party contract manufacturers. We are in the process of developing our supply chain for each of our product candidates and intend to put in place framework agreements under which third-party contract manufacturers will generally provide us with necessary quantities of API and drug product on a project-by-project basis based on our development needs. As we advance our product candidates through development, we will consider our lack of redundant supply for the API and drug product for each of our product candidates to protect against any potential supply disruptions through the use of a safety stock strategy and/or contracting with additional suppliers. However, we may be unsuccessful in putting in place such framework agreements or protecting against potential supply disruptions.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the U.S. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, EMA or comparable regulatory authorities, they will not be able to secure and/or maintain marketing approval for their manufacturing facilities. In addition, we do not have control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA, EMA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we will need to find alternative manufacturing facilities, and those new facilities would need to be inspected and approved by FDA, EMA or comparable regulatory authority prior to commencing manufacturing, which would significantly impact our ability to develop, obtain marketing approval for or market our product candidates, if approved. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or drugs, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates or drugs and harm our business and results of operations.

If any third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to enter into an agreement with a different third-party manufacturer, which we may not be able to do on reasonable terms, if at all. As a result, our clinical trials supply could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our product candidates may be unique or proprietary to the original third-party manufacturer and we may have difficulty, or there may be contractual

restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change third-party manufacturers for any reason, we will be required to verify that the new third-party manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product candidate according to the specifications previously submitted to the FDA or another regulatory authority. The delays associated with the verification of a new third-party manufacturer could negatively affect our ability to develop product candidates or commercialize our anticipated products in a timely manner or within budget. Furthermore, a third-party manufacturer may possess technology related to the manufacture of our product candidate that such third-party manufacturer owns independently. This would increase our reliance on such third-party manufacturer or require us to obtain a license from them in order to have another third-party manufacturer manufacture our product candidates. In addition, changes in manufacturers often involve changes in manufacturing procedures and processes, which could require that we conduct bridging studies between our prior clinical supply used in our clinical trials and that of any new manufacturer. We may be unsuccessful in demonstrating the comparability of clinical supplies which could require the conduct of additional clinical trials. Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

Our manufacturing process needs to comply with FDA regulations relating to the quality and reliability of such processes. Any failure to comply with relevant regulations could result in delays in or termination of our clinical programs and suspension or withdrawal of any regulatory approvals.

In order to commercially produce our products either at a third party's facility or in any facility of ours, we will need to comply with the FDA's cGMP regulations and guidelines. We may encounter difficulties in achieving quality control and quality assurance and may experience shortages in qualified personnel. We are subject to inspections by the FDA and comparable foreign regulatory authorities to confirm compliance with applicable regulatory requirements. Any failure to follow cGMP or other regulatory requirements or delay, interruption or other issues that arise in the manufacture, fill-finish, packaging, or storage of our precision medicines as a result of a failure of our facilities or the facilities or operations of third parties to comply with regulatory requirements or pass any regulatory authority inspection could significantly impair our ability to develop and commercialize our product candidates, including leading to significant delays in the availability of our precision medicines for our clinical trials or the termination of or suspension of a clinical trial, or the delay or prevention of a filing or approval of marketing applications for our product candidates. Significant non-compliance could also result in the imposition of sanctions, including warning or untitled letters, fines, injunctions, civil penalties, failure of regulatory authorities to grant marketing approvals for our product candidates, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of products, operating restrictions and criminal prosecutions, any of which could damage our reputation and our business.

If we engage in future acquisitions or strategic partnerships, this may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

From time to time, we evaluate various acquisition opportunities and strategic partnerships, including licensing or acquiring complementary products, product candidates, intellectual property rights, technologies or businesses. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- the issuance of our equity securities;
- assimilation of operations, intellectual property, products and product candidates of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing programs and initiatives in pursuing such a strategic merger or acquisition;

- retention of key employees, the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products, product candidates and marketing approvals; and
- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we undertake acquisitions or pursue partnerships in the future, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense.

If our third-party manufacturers use hazardous materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of potentially hazardous substances, including chemical materials, by our third-party manufacturers. Our manufacturers are subject to federal, state and local laws and regulations in the U.S. and local laws in other foreign jurisdictions governing the use, manufacture, storage, handling and disposal of medical and hazardous materials. Although we believe that our manufacturers' procedures for using, handling, storing and disposing of these materials comply with legally prescribed standards, we cannot completely eliminate the risk of contamination or injury resulting from medical or hazardous materials. As a result of any such contamination or injury, we may incur liability or local, city, state, federal or foreign authorities may curtail the use of these materials and interrupt our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. We do not have any insurance for liabilities arising from medical or hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, prospects, financial condition or results of operations.

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

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. We may seek to selectively form collaborations to expand our capabilities, potentially accelerate research and development activities and provide for commercialization activities by third parties. Any of these relationships may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business.

We face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Whether we reach a definitive agreement for a collaboration depends, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of preclinical studies or clinical trials, the likelihood of approval by the FDA, EMA or comparable foreign regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of intellectual property and industry and market conditions generally. The potential collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. Further, we may not be successful in our efforts to establish a collaboration or other alternative arrangements for product candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view them as having the requisite potential to demonstrate safety and efficacy.

In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. Even if we are successful in entering into a collaboration, the terms and conditions of that collaboration may restrict us from entering into future agreements on certain terms with potential collaborators.

If and when we seek to enter into collaborations, we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other discovery programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

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

If we enter into any collaboration arrangements with any third parties for the development and commercialization of our product candidates, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements. Collaborations 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 deemphasize 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 business combination or 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 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;
- we may grant exclusive rights to our collaborators that would prevent us from collaborating with others;
- 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 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;
- collaborators may not provide us with timely and accurate information regarding development progress and activities under the collaboration or may limit our ability to share such information, which could adversely impact our ability to report progress to our investors and otherwise plan our own development of our product candidates;
- collaborators may own or co-own intellectual property covering our products or product candidates that result from our collaborating with them, and in such cases, we would not have the exclusive right to develop or commercialize such intellectual property; and
- a collaborator's sales and marketing activities or other operations may not be in compliance with applicable laws resulting in civil or criminal proceedings.

Risks related to ownership of our common stock

The market price of our Class A common stock may be volatile, and our investors could lose all or part of their investment.

The trading price of our Class A common stock is likely to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. The stock market in general, and pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Broad market and industry factors may negatively affect the market price of our Class A common stock, regardless of our actual operating performance. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report, these factors include:

- the timing and results of INDs, preclinical studies and clinical trials of our product candidates or those of our competitors;
- the success of competitive products or announcements by potential competitors of their product development efforts;
- regulatory actions with respect to our products or product candidates or our competitors' products or product candidates;
- actual or anticipated changes in our growth rate relative to our competitors;
- regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures, collaborations or capital commitments;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- market conditions in the pharmaceutical and biotechnology sector;
- changes in the structure of healthcare payment systems;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;

- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- expiration of market stand-off or lock-up agreements;
- the impact of any natural disasters or public health emergencies, such as the ongoing COVID-19 pandemic; and
- general economic, political, industry and market conditions.

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 Class A common stock.

If securities or industry analysts do not publish research or reports, or if they publish adverse or misleading research or reports, regarding us, our business or our market, our stock price and trading volume could decline.

The trading market for our Class A common stock may be influenced by the research and reports that securities or industry analysts publish about us, our business or our market. We do not currently have and may never obtain research coverage by securities or industry analysts. If no or few securities or industry analysts commence coverage of us, our stock price would be negatively impacted. In the event we obtain securities or industry analyst coverage, if any of the analysts who cover us issue adverse or misleading research or reports regarding us, our business model, our intellectual property, our stock performance or our market, or if our operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of these 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 our stock price or trading volume to decline.

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.

Our quarterly and annual operating results may fluctuate significantly in the future, which makes it difficult for us to predict our future operating results. From time to time, we may enter into license or collaboration agreements or strategic partnerships with other companies that include development funding and significant upfront and milestone payments and/or royalties, which may become an important source of our revenue. These upfront and milestone payments may vary significantly from period to period and any such variance could cause a significant fluctuation in our operating results from one period to the next.

In addition, we measure compensation cost for stock-based awards made to employees at the grant date of the award, based on the fair value of the award as determined by our board of directors, and recognize the cost as an expense over the employee's requisite service period. As the variables that we use as a basis for valuing these awards change over time, our underlying stock price and stock price volatility, the magnitude of the expense that we must recognize may vary significantly.

Furthermore, our operating results may fluctuate due to a variety of other factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and cost of, and level of investment in, research and development activities relating to our programs, which will change from time to time;
- our ability to enroll patients in clinical trials and the timing of enrollment;
- the cost of manufacturing our current product candidates and any future product candidates, which may vary depending on FDA, EMA or other comparable foreign regulatory authority guidelines and requirements, the quantity of production and the terms of our agreements with manufacturers;
- expenditures that we will or may incur to acquire or develop additional product candidates and technologies or other assets;

- the timing and outcomes of preclinical studies and clinical trials for NVL-520 and NVL-655, and any product candidates from our discovery programs, or competing product candidates;
- the need to conduct unanticipated clinical trials or trials that are larger or more complex than anticipated;
- competition from existing and potential future products that compete with NVL-520 or NVL-655 or any of our discovery programs, and changes in the competitive landscape of our industry, including consolidation among our competitors or partners;
- any delays in regulatory review or approval of NVL-520 and NVL-655 or product candidates from any of our discovery programs;
- the level of demand for any of our product candidates, if approved, which may fluctuate significantly and be difficult to predict;
- the risk/benefit profile, cost and reimbursement policies with respect to our product candidates, if approved, and existing and potential future products that compete with NVL-520 and NVL-655, or any of our discovery programs;
- our ability to commercialize NVL-520 or NVL-655, or product candidates from any of our discovery programs, if approved, inside and outside of the U.S., either independently or working with third parties;
- our ability to establish and maintain collaborations, licensing or other arrangements;
- our ability to adequately support future growth;
- potential unforeseen business disruptions that increase our costs or expenses;
- future accounting pronouncements or changes in our accounting policies; and
- the changing and volatile global economic and political environment.

The cumulative effect of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our Class A common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated guidance we may provide.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have experienced extreme volatility and disruptions in the past several years, most recently due to the ongoing COVID-19 pandemic, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions, whether due to the evolving effects of the COVID-19 pandemic or otherwise, will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive.

Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse event on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our

ability to attain our operating goals on schedule and on budget. Our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval. Three of our directors are affiliated with our principal stockholders.

Our executive officers, directors, holders of 5% or more of our capital stock and their respective affiliates beneficially own approximately 66.7% of our outstanding Class A common stock and Class B common stock and 62.4% of our Class A voting stock (based on the number of shares of common stock outstanding as of December 31, 2021). Three of our directors are affiliated with two of our principal stockholders, including Joseph Pearlberg, M.D., Ph.D. and Cameron A. Wheeler, Ph.D. who are affiliated with Deerfield, and Andrew A.F. Hack, M.D., Ph.D. who is affiliated with Bain Capital Life Sciences. These stockholders, acting together, may be able to impact matters requiring stockholder approval. For example, they may be able to impact elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that investors may feel are in their best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with each investor's 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 Class A common stock.

The dual class structure of our common stock and the option of the holders of shares of our Class B common stock to convert into shares of our Class A common stock may limit our Class A common stockholders' ability to influence corporate matters.

Our Class A common stock has one vote per share, while our Class B common stock is non-voting. Nonetheless, each share of our Class B common stock may be converted at any time into one share of Class A common stock at the option of its holder, subject to the limitations provided for in our third amended and restated certificate of incorporation that prohibit the conversion of our Class B common stock into shares of Class A common stock to the extent that, upon such conversion, such holder and any other persons with whom such holder's beneficial ownership would be aggregated for purposes of Section 13(d) of the Exchange Act would beneficially own in excess of 4.9% or 9.9%, as applicable, based on the holder's election of any class of our securities registered under the Exchange Act. Consequently, if holders of Class B common stock exercise their option to make this conversion, such exercise will have the effect of increasing the relative voting power of those prior holders of our Class B common stock (subject to the ownership limitation described in the previous sentence) and increasing the number of outstanding shares of our voting common stock, and correspondingly decreasing the relative voting power of the current holders of our Class A common stock, which may limit our Class A common stockholders' ability to influence corporate matters. Because our Class B common stock is generally non-voting, stockholders who own more than 10% of our common stock overall but 10% or less of our Class A common stock will not be required to report changes in their ownership from transactions in our common stock pursuant to Section 16(a) of the Exchange Act and would not be subject to the short-swing profit provisions of Section 16(b) of the Exchange Act.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our 2021 Stock Plan, could result in dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital may be needed in the future to continue our planned operations, including conducting clinical trials, commercialization efforts, expanded research and development activities and costs associated with operating a public company. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities, investors may be materially diluted by such sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to the holders of our common stock.

Pursuant to our 2021 Stock Plan, our management is authorized to grant stock options to our employees, directors and consultants. If the number of shares reserved under our 2021 Stock Plan is increased pursuant to the terms of the 2021 Stock Plan, our stockholders may experience dilution, which could cause our stock price to fall.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and could involve certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through future strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates or grant licenses on terms unfavorable to us.

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 and 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 intend to take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure in our periodic reports;
- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended (the Sarbanes-Oxley Act);
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements; and
- exemptions from the requirements of holding nonbinding advisory stockholder votes on executive compensation and stockholder approval of any golden parachute payments not previously approved.

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 avail ourselves of this exemption from 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 the new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest to occur of: (i) the last day of the fiscal year in which we have more than $1.07 billion in annual revenue; (ii) the date we qualify as a "large accelerated filer," with at least $700.0 million of equity securities held by non-affiliates; (iii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period; and (iv) the last day of the fiscal year ending after the fifth anniversary of our IPO.

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 continue 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 and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our Class A common stock less attractive because we may rely on these exemptions.

We have increased costs as a result of operating as a public company, and our management is devoting substantial time to related compliance initiatives.

As a public company, we are incurring significant legal, accounting and other expenses, and these expenses may increase even more after we are no longer an "emerging growth company." We will be subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, and the Dodd-Frank Wall Street Reform and Protection Act, as well as rules adopted, and to be adopted, by the SEC and Nasdaq. Our management and other personnel 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, which will increase our operating expenses. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain sufficient coverage, particularly in light of recent cost increases related to coverage. We cannot accurately 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.

In addition, as a public company we are required to incur additional costs and obligations in order to comply with SEC rules that implement Section 404 of the Sarbanes-Oxley Act. Under these rules, beginning with our second annual report on Form 10-K, we will be required to make a formal assessment of the effectiveness of our internal control over financial reporting, and once we cease to be an emerging growth company, we may be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaging in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of our internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are designed and operating effectively, and implement a continuous reporting and improvement process for internal control over financial reporting.

If we experience material weaknesses in the future or otherwise fail to maintain an effective system of internal controls in the future, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

We may in the future discover material weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. 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.

We, and our independent registered public accounting firm, were not required to perform an evaluation of our internal control over financial reporting as of December 31, 2021 in accordance with the provisions of the Sarbanes-Oxley Act. Accordingly, we cannot assure our stockholders' that we will not in the future identify material weaknesses. Material weaknesses may exist when we become required to report on the effectiveness of our internal control over financial reporting under Section 404 of the Sarbanes-Oxley Act.

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 over financial reporting, we may not be able to produce timely and accurate financial statements. If that were to happen, our investors could lose confidence in our reported financial information, the market price of our stock could decline, and we could be subject to sanctions or investigations by the stock exchange on which our Class A common stock is listed, the SEC or other regulatory authorities.

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

We are subject to the periodic reporting requirements of the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the facts that judgments in decision-making can be faulty and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

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

The market price of our Class A common stock may be volatile and, 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.

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

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to any appreciation in the value of their stock.

Anti-takeover provisions in our certificate of incorporation and bylaws and Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the market price of our Class A common stock.

Our third amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could depress the market price of our common stock by acting to discourage, delay or prevent a change in control of our company or changes in our management that the stockholders of our company may deem advantageous. These provisions, among other things:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder actions through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of stockholders be called only by our board of directors acting pursuant to a resolution approved by the affirmative vote of a majority of the directors then in office;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors;

- a requirement of approval of not less than two-thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action or to amend specific provisions of our certificate of incorporation; and
- the authority of our board of directors to issue preferred stock on terms determined by our board of directors without stockholder approval and which preferred stock may include rights superior to the rights of the holders of common stock.

In addition, Section 203 of the General Corporation Law of the State of Delaware (the DGCL), prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

Any provision of our third amended and restated certificate of incorporation, amended and restated bylaws or Delaware law that has the effect of delaying or preventing a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our capital stock and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws designate certain courts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of, or a claim based on, fiduciary duty owed by any of our current or former directors, officers, and employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the DGCL, our certificate of incorporation or our amended and restated bylaws or (iv) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein (the Delaware Forum Provision). The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act, or the Exchange Act. Our amended and restated bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the U.S. shall be the sole and exclusive forum for resolving any complaint asserting a cause or causes of action arising under the Securities Act (the Federal Forum Provision). In addition, our amended and restated bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the foregoing provisions; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

The Delaware Forum Provision and the Federal Forum Provision in our amended and restated bylaws may impose additional litigation costs on stockholders in pursuing any such claims. Additionally, the forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. In addition, while the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court were "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. If the Federal Forum Provision is found to be unenforceable, we may incur additional costs associated with resolving such matters. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is not enforceable or invalid. The Court of Chancery of the State of Delaware and the federal district courts of the U.S. may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our corporate headquarters are located in Cambridge, Massachusetts, where we lease office space pursuant to a month-to month lease. We believe that this existing facility is adequate for our current needs and that suitable additional or alternative space will be available in the future on commercially reasonable terms, if required.

ITEM 3. LEGAL PROCEEDINGS

As of December 31, 2021, we were not party to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Certain Information Regarding the Trading of Our Common Stock

Our Class A common stock trades under the symbol "NUVL" on the Nasdaq Global Select Market and has been publicly traded since July 29, 2021. Prior to this time, there was no public market for our Class A common stock. Our Class B common stock is not listed or traded on any stock exchange.

Holders of Our Common Stock

As of February 28, 2022, there were approximately 34 holders of record of shares of our Class A common stock and 2 holders of record of shares of our Class B common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

Recent Sales of Unregistered Securities

There are no shares of equity securities sold or issued, or options granted, by us during the year ended December 31, 2021 that were not registered under the Securities Act of 1933, as amended, or the Securities Act, and that were not previously reported in a Quarterly Report on Form 10-Q or Current Report on Form 8-K.

Use of Proceeds from the Initial Public Offering

On August 2, 2021, we completed our IPO pursuant to which we issued and sold 10,612,500 shares of Class A common stock, including the exercise in full by the underwriters of their option to purchase up to 1,462,500 additional shares of Class A common stock, and 600,000 shares of Class B common stock, at a public offering price of $17.00 per share. All of the shares of Class A common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (Registration No. 333-256949), which was declared effective by the SEC on July 28, 2021. J.P. Morgan Securities LLC, Cowen and Company, LLC and Piper, Sandler & Co. acted as joint book-running managers for the offering. Each share of Class B common stock may be converted at any time into one share of Class A common stock at the option of its holder, subject to the ownership limitations provided for in our amended and restated certificate of incorporation. The aggregate gross proceeds to us from our IPO, inclusive of the underwriters' option to purchase additional shares, were $190.6 million.

The aggregate net proceeds to us from the IPO, inclusive of the underwriters' option to purchase additional shares, was approximately $174.3 million, after deducting underwriting discounts and commissions and offering expenses payable by us of approximately $16.4 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

As of December 31, 2021, we have used approximately $20.6 million of the net offering proceeds from the IPO. There has been no material change in our planned use of the net proceeds from the offering as described in our final prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC pursuant to Rule 424(b)(4) under the Securities Act of 1933, as amended, on July 30, 2021.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period from October 1, 2021 to December 31, 2021.

Dividends

We have never declared or paid cash dividends on our common stock since our inception. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

ITEM 6. [RESERVED]

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes appearing at the end of this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. For a detailed discussion on our business environment, please read Item 1. Business, included in this Annual Report. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis.

Overview

We are a clinical stage biopharmaceutical company focused on creating *precisely* targeted therapies for patients with cancer. We leverage our team's deep expertise in chemistry and structure-based drug design to develop innovative small molecules that are designed with the aim to overcome the limitations of existing therapies for clinically proven kinase targets. Through addressing the limitations of existing therapies, we believe our programs have the potential to drive deeper, more durable responses with minimal adverse events. We believe these potential benefits will support opportunities for clinical utility earlier in the treatment paradigm.

We focus our discovery efforts on small molecule inhibitors of kinases, a class of cellular targets that can play a central role in cancer growth and proliferation. In particular, we focus on "clinically proven" kinase targets, or those for which therapies have been developed by others to target those kinases, and that such drugs have demonstrated sufficient clinical efficacy and safety data to be approved by the FDA or similar regulatory agency and are established and used in the clinical setting. Currently available kinase inhibitors face multiple limitations, which can include kinase resistance, or the emergence of new mutations in the kinase target that can enable resistance to existing therapies, kinase selectivity, or the potential for existing therapies to inhibit other structurally similar kinase targets and lead to off-target adverse events, and limited brain penetrance, or the ability for the therapy to treat disease that has spread or metastasized to the brain. By prioritizing target selectivity, we believe our drug candidates have the potential to overcome resistance, minimize adverse events, optimize brain penetrance to address brain metastases, and drive more durable responses.

We are advancing a robust pipeline of product candidates with parallel lead programs in cancers driven by genomic alterations in the ROS1 and ALK kinases (*i.e.,* ROS1-positive and ALK-positive, respectively), along with multiple discovery-stage research programs. We hold worldwide development and commercialization rights to our product candidates.

Our first lead product candidate, NVL-520, is a novel ROS1-selective inhibitor designed with the aim to address the clinical challenges of emergent treatment resistance, CNS-related adverse events, and brain metastases that may limit the use of currently available ROS1 TKI. Preclinical data has shown that NVL-520 was brain-penetrant, inhibited wild-type ROS1 fusions, remained active in the presence of mutations conferring resistance to approved and investigational ROS1 inhibitors, and displayed strong selectivity for both wild-type ROS1 and its resistance variants as compared to the structurally related TRKB, thereby minimizing the potential for off-target TRKB-related CNS adverse events.

We are currently enrolling patients in the Phase 1 portion of our ARROS-1 clinical trial, a first-in-human Phase 1/2, multicenter, open-label, dose-escalation and expansion study evaluating NVL-520 as an oral monotherapy in patients with advanced ROS1-positive NSCLC and other solid tumors. ARROS-1 is comprised of two study components, beginning with a Phase 1 dose-escalation portion to evaluate the safety and tolerability of NVL-520 in patients with advanced ROS1-positive solid tumors previously treated with at least one ROS1 TKI, as well as to determine the RP2D, characterize the pharmacokinetic profile, and evaluate preliminary anti-tumor activity of NVL-520. Once the RP2D is determined, the study may transition directly into a Phase 2 portion designed to support potential registration of NVL-520 in both ROS1-positive patients with NSCLC who are TKI-naïve and who have been previously treated with ROS1 kinase inhibitors.

Our second lead product candidate, NVL-655, is a brain-penetrant ALK-selective inhibitor, designed with the aim to address the clinical challenges of emergent treatment resistance, CNS-related adverse events, and brain metastases that may limit the use of first-, second-, and third-generation ALK inhibitors. Preclinical data has shown that NVL-655 was brain-penetrant, inhibited wild-type ALK fusions, remained active in the presence of mutations conferring resistance to approved and investigational ALK inhibitors, and displayed strong selectivity for both wild-type ALK and its resistance variants as compared to the structurally related TRKB, thereby minimizing the potential for off-target TRKB-related CNS adverse events. We have submitted an IND for NVL-655 and the FDA has confirmed that clinical investigation of NVL-655 may proceed. We plan to initiate the ALKOVE-1 study, a first-in-human Phase 1/2, multicenter, open-label, dose escalation and expansion study investigating NVL-655 in advanced ALK-positive NSCLC and other solid tumors, in the second quarter of 2022.

In addition to our lead programs, we have prioritized a number of additional small molecule research programs following an assessment of medical need, including a second ALK inhibitor program designed with the aim to address emerging compound resistance mutations and a HER2 Exon 20 insertions program. We expect to nominate product candidates for these programs in 2022.

Since commencing significant operations in 2018, we have focused substantially all of our efforts and financial resources on research and development activities for our programs, including NVL-520 and NVL-655, establishing and maintaining our intellectual property portfolio, organizing and staffing our company, business planning, raising capital, and providing general and administrative support for these operations. We do not have any products approved for sale and have not generated revenue from product sales or any other source. To date, we have funded our operations primarily with proceeds from the sales of Series A and Series B convertible preferred stock, the issuance of convertible notes (which converted to convertible preferred stock in 2018), debt financing from stockholders (which was settled in convertible preferred stock in February 2021), and most recently, with proceeds from the sale of common stock in the IPO completed in August 2021.

On August 2, 2021, we completed an IPO of our common stock pursuant to which we issued and sold 10,612,500 shares of Class A common stock and 600,000 shares of Class B common stock, including the exercise in full by the underwriters of their option to purchase 1,462,500 additional shares of Class A common stock, at a public offering price of $17.00 per share. We received net proceeds of approximately $174.3 million after deducting underwriting discounts and commissions and offering costs.

Since our inception, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of our product candidates. We reported net losses of $46.3 million and $14.6 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $78.2 million. We expect to incur significant expenses at an increasing rate and increasing operating losses for the foreseeable future. We expect our expenses and capital requirements will increase substantially in connection with ongoing activities, particularly if and as we:

- continue to advance our NVL-520 program in clinical development;
- advance our NVL-655 program from preclinical development into clinical development;
- advance the development of our discovery programs, including our ALK IXDN and HER2 programs;
- expand our pipeline of product candidates through our own product discovery and development efforts;
- seek to discover and develop additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any approved product candidates and related additional commercial manufacturing costs;
- implement operational, financial and management systems;

- attract, hire and retain additional clinical, scientific, management and administrative personnel;
- maintain, expand, protect and enforce our intellectual property portfolio, including patents, trade secrets and know how;
- acquire or in-license other product candidates and technologies; and
- operate as a public company.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. If we obtain regulatory approval for any of our product candidates and do not enter into a commercialization partnership, we expect to incur significant expenses related to developing our internal commercialization capability to support product sales, marketing and distribution. Further, we expect to incur additional costs associated with operating as a public company.

As a result, we will need substantial additional funding 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 expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and the disruptions to, and volatility in, the credit and financial markets in the U.S. and worldwide resulting from the ongoing COVID-19 pandemic and otherwise. Our failure to obtain sufficient funds on acceptable terms when needed could have a material adverse effect on our business, results of operations or financial condition, including requiring us to have to delay, reduce or eliminate our product development or future commercialization efforts. Insufficient liquidity may also require us to relinquish rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our development efforts.

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 or when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements into 2024. Our existing cash, cash equivalents and marketable securities will not be sufficient to fund any of our product candidates through regulatory approval, and we anticipate needing to raise additional capital to complete the development and commercialization of our product candidates. See *"—Liquidity and Capital Resources."*

The global COVID-19 pandemic continues to rapidly evolve. The extent of the impact of the COVID-19 pandemic on our business, operations and development timelines and plans remains uncertain, and will depend on certain developments, including the duration and spread of the outbreak and its impact on our development activities, clinical trial enrollment, future trial sites, CROs, third-party manufacturers, and other third parties with whom we do business, as well as its impact on regulatory authorities and our key scientific and management personnel. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. To the extent possible, we are conducting business as usual, with necessary or advisable modifications to employee travel and with our employees working remotely. While we have opened our office for use under strict guidelines as required by federal, state, and local authorities, the majority of our employees are remote. We will continue to actively monitor the rapidly evolving situation related to COVID-19 and may take further actions that alter our operations, including those that may be required by federal, state or local authorities, or that we determine are in the best interests of our employees and other third parties with whom we do business. At this point, the extent to which the COVID-19 pandemic may affect our business, operations and development timelines and plans, including the resulting impact on our expenditures and capital needs, and on our ability to initiate and conduct clinical trials in the timelines we expect, remains uncertain.

Components of Our Results of Operations

Operating expenses

Our operating expenses are comprised of research and development expenses and general and administrative expenses.

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- personnel-related costs, including salaries, benefits and stock-based compensation expense, for employees engaged in research and development functions;
- expenses incurred in connection with our research programs, including under agreements with third parties, such as consultants and contractors and CROs;
- the cost of developing and scaling our manufacturing process and manufacturing drug substance and drug product for use in our research and preclinical and clinical studies, including under agreements with third parties, such as consultants and contractors and CMOs; and
- the cost of laboratory supplies and research materials.

We track our direct external research and development expenses on a program-by-program basis. These consist of costs that include fees, reimbursed materials, and other costs paid to consultants, contractors, CMOs, and CROs in connection with our preclinical, clinical and manufacturing activities. We do not allocate employee costs, costs associated with our discovery efforts, and facilities expenses, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple programs and, as such, are not separately classified.

We expect that our research and development expenses will increase substantially as we continue to advance NVL-520 in clinical development and plan to advance NVL-655 into clinical development and expand our discovery, research and preclinical activities in the near term and in the future. Although we are currently enrolling patients in the Phase 1 portion of our ARROS-1 clinical trial and we plan to initiate the Phase 1/2 trial for our ALK program in the second quarter of 2022, at this time, we cannot accurately estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any product candidates we may develop. A change in the outcome of any number of variables with respect to product candidates we may develop could significantly change the costs and timing associated with the development of that product candidate. The duration, costs and timing of preclinical studies and clinical trials and development of our product candidates will depend on a variety of factors, including:

- the timing and progress of development activities relating to NVL-520, NVL-655 and any future product candidates from our ALK IXDN, HER2 and other discovery programs, including any additional costs that may result from delays in enrollment or other factors;
- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to maintain our current research and development programs and to establish new ones;
- establishing an appropriate safety profile with IND-enabling toxicology studies;
- successful patient enrollment in, and the initiation and completion of, clinical trials;
- the number of trials required for regulatory approval;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible subjects and initial clinical trials;
- the number of subjects that participate in the trials and per subject trial costs;

- potential additional safety monitoring requested by regulatory authorities;
- the duration of subject participation in the trials and follow-up;
- the successful completion of clinical trials with safety, tolerability and efficacy profiles that are satisfactory to applicable regulatory authorities;
- the receipt of regulatory approvals from applicable regulatory authorities;
- the timing, receipt and terms of any marketing approvals and post-marketing approval commitments from applicable regulatory authorities;
- the extent to which we establish collaborations, strategic partnerships or other strategic arrangements with third parties, if any, and the performance of any such third party;
- establishing commercial manufacturing capabilities or making arrangements with CMOs;
- development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials and for commercial launch; and
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights.

Any changes in the outcome of any of these factors could significantly impact the costs, timing and viability associated with the development of our product candidates. For example, if the FDA or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate.

General and administrative expenses

General and administrative expenses consist primarily of salaries and related costs, including stock-based compensation, for personnel in executive, finance and administrative functions. General and administrative expenses also include professional fees for legal, patent, consulting, investor and public relations and accounting and audit services. We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance, and director and officer insurance costs as well as investor and public relations expenses associated with operating as a public company.

Other income (expense)

Change in fair value of preferred stock tranche rights

Pursuant to the terms of our Series A Preferred Stock Purchase Agreement, we provided investors with the right and obligation to participate in subsequent closings of Series A convertible preferred stock upon the achievement of certain strategic milestones or as determined by the Series A investors (the Series A Tranche Rights). These Series A Tranche Rights met the definition of a freestanding financial instrument as the Series A Tranche Rights were legally detachable and separately exercisable from the Series A convertible preferred stock. The Series A Tranche Rights were initially classified as a liability on our consolidated balance sheet that we remeasured to fair value at each reporting date, and we recognized changes in fair value of the Series A Tranche Rights as a component of other income (expense) in our consolidated statements of operations and comprehensive loss. All Series A Tranche Rights were settled by March 31, 2021.

Other income (expense), net

Other income (expense), net, consists of interest income, interest expense and other income (expense) unrelated to our core operations.

Income taxes

Since our inception, we have not recorded income tax benefits for the net operating losses incurred or the research and development tax credits generated in each year, due to the uncertainty of realizing a benefit from those items.

As of December 31, 2021, we had U.S. federal and state net operating loss carryforwards of $73.2 million and $72.5 million, respectively, which may be available to offset future taxable income. The federal net operating loss carryforwards include $1.1 million which expire in 2037 and $72.1 million which carryforward indefinitely, but may only be used to offset 80% of annual taxable income. The state net operating loss carryforwards expire at various dates beginning in 2037. As of December 31, 2021, we also had federal and state research and development tax credit carryforwards of $1.6 million and $0.7 million, respectively, which may be available to offset future tax liabilities and expire at various dates beginning in 2033.

Results of Operations

Comparison of the Years Ended December 31, 2021 and 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020:

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Operating expenses:			
Research and development	$ 35,559	$ 15,403	$ 20,156
General and administrative	10,258	1,502	8,756
Total operating expenses	45,817	16,905	28,912
Loss from operations	(45,817)	(16,905)	(28,912)
Other income (expense):			
Change in fair value of preferred stock tranche rights	(635)	2,384	(3,019)
Other income (expense), net	114	(35)	149
Total other income (expense), net	(521)	2,349	(2,870)
Net loss	$ (46,338)	$ (14,556)	$ (31,782)

Research and development expenses

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Direct research and development expenses by program:			
NVL-520	$ 11,411	$ 4,583	$ 6,828
NVL-655	7,302	2,948	4,354
Discovery programs	7,388	3,835	3,553
Unallocated research and development expenses:			
Personnel-related (including stock-based compensation)	8,067	3,024	5,043
Other	1,391	1,013	378
Total research and development expenses	$ 35,559	$ 15,403	$ 20,156

Research and development expenses were $35.6 million for the year ended December 31, 2021, compared to $15.4 million for the year ended December 31, 2020. The increase in direct research and development expenses related to NVL-520 of $6.8 million was primarily due to increased manufacturing and clinical costs, partially offset by a decrease in preclinical costs as we progressed NVL-520 and prepared for the Phase 1 portion of our

ARROS-1 clinical trial. The increase in direct research and development expenses related to NVL-655 of $4.4 million was primarily due to increased manufacturing and clinical costs to support our planned clinical trial and increased costs for IND-enabling studies, partially offset by a decrease in preclinical costs as we progressed NVL-655. The increase in direct research and development expenses related to our discovery programs of $3.6 million was primarily due to an increase in preclinical costs due to progress of our discovery programs. The increase in personnel-related expenses of $5.0 million was primarily due to an increase in headcount. Personnel-related costs for the years ended December 31, 2021 and 2020 included stock-based compensation expense of $1.3 million and $0.7 million, respectively.

General and administrative expenses

	Year Ended December 31,		
	2021	2020	Change
		(in thousands)	
Personnel-related (including stock-based compensation)	$ 5,131	$ 797	$ 4,334
Professional and consultant fees	3,095	525	2,570
Other	2,032	180	1,852
Total general and administrative expenses	$ 10,258	$ 1,502	$ 8,756

General and administrative expenses were $10.3 million for the year ended December 31, 2021, compared to $1.5 million for the year ended December 31, 2020. The increase in personnel-related costs of $4.3 million was primarily due to an increase in headcount. Personnel-related costs for the years ended December 31, 2021 and 2020 included stock-based compensation expense of $2.2 million and less than $0.1 million, respectively. The increase in professional and consultant fees of $2.6 million was primarily due to increased legal and audit fees associated with operating as a public company and our ongoing business activities. The increase in other of $1.9 million was primarily due to increased insurance and recruiting expenses associated with operating as a public company and to support our growing organization.

Other income (expense)

Change in fair value of preferred stock tranche rights

The change in the fair value of the Series A Tranche Rights for the year ended December 31, 2021, compared to the year ended December 31, 2020 was primarily due to the change in the fair value of our preferred stock during that period.

Liquidity and Capital Resources

Since our inception, we have incurred significant operating losses. We have not yet commercialized any of our product candidates and we do not expect to generate revenue from sales of any product candidates for the foreseeable future, if at all. Through December 31, 2021, we have funded our operations primarily with proceeds from the sales of Series A and Series B convertible preferred stock, the issuance or convertible notes (which converted to convertible preferred stock in 2018), debt financing from stockholders (which was settled in convertible preferred stock in February 2021) and most recently, with proceeds from the sale of common stock in the IPO completed in August 2021. As of December 31, 2021, we had cash, cash equivalents and marketable securities of $288.1 million.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Net cash used in operating activities	$ (40,000)	$ (14,949)
Net cash used in investing activities	(220,028)	—
Net cash provided by financing activities	318,222	22,265
Net increase in cash and cash equivalents	$ 58,194	$ 7,316

Operating activities

During the year ended December 31, 2021, operating activities used $40.0 million of cash, primarily resulting from our net loss of $46.3 million, partially offset by net non-cash charges of $4.4 million and net cash provided by changes in our operating assets and liabilities of $1.9 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2021, consisted primarily of a $5.4 million increase in accounts payable and accrued expenses, partially offset by an increase of $3.2 million in other assets.

During the year ended December 31, 2020, operating activities used $14.9 million of cash, resulting from our net loss of $14.6 million and net non-cash income of $1.7 million, partially offset by net cash provided by changes in our operating assets and liabilities of $1.3 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2020, consisted primarily of an increase in accounts payable and accrued expenses and other current liabilities of $1.3 million.

Changes in accounts payable, accrued expenses and other current liabilities, prepaid expenses and other current assets and other assets were generally due to growth in our business, the advancement of our research programs and the timing of vendor invoicing and payments.

Investing activities

During the year ended December 31, 2021, net cash used in investing activities was $220.0 million, due to the purchases of marketable securities during the period, partially offset by sales and maturities of marketable securities.

Financing activities

During the year ended December 31, 2021, net cash provided by financing activities was $318.2 million, consisting of proceeds from our IPO, net of underwriting discounts and commissions of $177.3 million and proceeds from the issuance of our Series A and Series B convertible preferred stock of $144.7 million, partially offset by payment of IPO costs of $3.0 million.

During the year ended December 31, 2020, net cash provided by financing activities was $22.3 million, consisting of proceeds from the issuance of our Series A convertible preferred stock, partially offset by the issuance of a promissory note to our scientific founder.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical and clinical activities and clinical trials for our product candidates in development. In addition, we expect to incur additional costs associated with operating as a public company. The timing and amount of our operating expenditures will depend largely on:

- the initiation, progress, timing, costs and results of preclinical studies and clinical trials for our discovery programs and product candidates, including the advancement of NVL-520 and planned advancement of NVL-655 throughout clinical development;
- the clinical development plans we establish for our product candidates;
- the number and characteristics of product candidates that we discover and develop through our product discovery and research efforts;
- the terms of any collaboration agreements we may choose to pursue;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA, the EMA and other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending intellectual property disputes, including patent infringement actions brought by third parties against us;

- the effect of competing technological and market developments;
- the cost and timing of completion of commercial-scale outsourced manufacturing activities; and
- the cost of establishing sales, marketing and distribution capabilities for any product candidates for which we may receive regulatory approval in regions where we choose to commercialize our products on our own.

As of December 31, 2021, we had cash, cash equivalents and marketable securities of $288.1 million. We expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements into 2024. Our existing cash, cash equivalents and marketable securities will not be sufficient to fund any of our product candidates through regulatory approval, and we anticipate needing to raise additional capital to complete the development and commercialization of our product candidates. Our estimate as to how long we expect our existing cash, cash equivalents and marketable securities to fund our operations is based on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical product candidates, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements will depend on and could increase significantly as a result of many factors, including those listed above.

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. We do not currently have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our common stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our 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.

Contractual Obligations and Other Commitments

We lease certain office space in Cambridge, Massachusetts pursuant to a month-to-month lease. We enter into contracts in the normal course of business with our CMOs, CROs and other third parties to support preclinical research studies and other research and development activities. These contracts are generally cancelable by us.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the U.S. (GAAP). The preparation of our consolidated financial statements and related disclosures requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our applicable personnel to identify services that have been performed on our behalf and estimating the level of services performed and the associated cost incurred for the services when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in the financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of the estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors in connection with preclinical development activities;
- CROs in connection with preclinical and clinical studies and testing; and
- CMOs in connection with the process development and scale up activities and the production of materials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CROs and CMOs that conduct services and supply materials. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses. While the majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met, some require advance payments. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. We record these as prepaid expenses on our consolidated balance sheet.

Stock-based compensation

We measure stock options with service-based vesting granted to employees, non-employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. We measure restricted common stock awards using the difference between the purchase price per share of the award, if any, and the fair value of our common stock at the date of grant. Compensation expense for the awards is recognized over the requisite service period, which is generally the vesting period of the respective award. We use the straight-line method to record the expense of awards with only service-based vesting conditions. We account for forfeitures of stock-based awards as they occur.

We classify stock-based compensation expense in our consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Recently Issued and Adopted Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our consolidated financial statements included in this Annual Report.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

NUVALENT, INC.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Nuvalent, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Nuvalent, Inc. and subsidiary (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for the years then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated 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 consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ KPMG LLP

We have served as the Company's auditor since 2020.

Boston, Massachusetts
March 29, 2022

NUVALENT, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share amounts)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 68,526	$ 10,332
Marketable securities	219,585	—
Prepaid expenses and other current assets	2,517	314
Total current assets	290,628	10,646
Other assets	3,196	—
Total assets	$293,824	$ 10,646
Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 2,893	$ 1,252
Accrued expenses	5,894	1,171
Preferred stock tranche rights	—	1,957
Total current liabilities	8,787	4,380
Notes payable and accrued interest to stockholder	—	2,235
Total liabilities	8,787	6,615
Commitments and contingencies (Note 11)		
Convertible preferred stock (Series A and B), $0.0001 par value; no shares and 112,431,508 shares authorized at December 31, 2021 and 2020, respectively; no shares and 89,945,206 shares issued and outstanding at December 31, 2021 and 2020, respectively;	—	35,354
Stockholders' equity (deficit):		
Preferred stock, $0.0001 par value; 10,000,000 shares and no shares authorized at December 31, 2021 and 2020, respectively; no shares issued or outstanding	—	—
Class A common stock, $0.0001 par value; 140,000,000 shares and 160,000,000 shares authorized at December 31, 2021 and 2020, respectively; 42,862,175 shares and 3,129,384 shares issued and outstanding at December 31, 2021 and 2020, respectively	4	—
Class B common stock, $0.0001 par value; 10,000,000 shares and no shares authorized at December 31, 2021 and 2020, respectively; 5,435,254 shares and no shares issued and outstanding at December 31, 2021 and 2020, respectively	1	—
Additional paid-in capital	363,483	842
Accumulated other comprehensive loss	(228)	—
Accumulated deficit	(78,223)	(31,885)
Promissory note from stockholder	—	(280)
Total stockholders' equity (deficit)	285,037	(31,323)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$293,824	$ 10,646

The accompanying notes are an integral part of these consolidated financial statements.

NUVALENT, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share amounts)

	Year Ended December 31,	
	2021	2020
Operating expenses:		
Research and development	$ 35,559	$ 15,403
General and administrative	10,258	1,502
Total operating expenses	45,817	16,905
Loss from operations	(45,817)	(16,905)
Other income (expense):		
Change in fair value of preferred stock tranche rights	(635)	2,384
Other income (expense), net	114	(35)
Total other income (expense), net	(521)	2,349
Net loss	$ (46,338)	$ (14,556)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.13)	$ (5.08)
Weighted average shares of common stock outstanding, basic and diluted	21,783,754	2,867,221
Comprehensive loss:		
Net loss	$ (46,338)	$ (14,556)
Other comprehensive loss:		
Unrealized losses on marketable securities, net of tax of $0	(228)	—
Comprehensive loss	$ (46,566)	$ (14,556)

The accompanying notes are an integral part of these consolidated financial statements.

NUVALENT, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share amounts)

	Convertible Preferred Stock		Class A Common Stock		Class B Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Promissory Note from Stockholder	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount					
Balances at December 31, 2019	39,351,028	$ 14,048	2,138,988	$—	—	$—	$ 98	$ —	$(17,329)	$ (25)	$ (17,256)
Issuance of Series A convertible preferred stock	50,594,178	22,500	—	—	—	—	—	—	—	—	—
Issuance of common stock	—	—	952,740	—	—	—	—	—	—	—	—
Issuance of common stock upon exercise of stock options	—	—	37,656	—	—	—	15	—	—	—	15
Issuance of promissory note from related party stockholder	—	—	—	—	—	—	—	—	—	(250)	(250)
Interest on promissory note from related party stockholder	—	—	—	—	—	—	—	—	—	(5)	(5)
Stock-based compensation expense	—	—	—	—	—	—	729	—	—	—	729
Reclassification of preferred stock tranche rights upon settlement	—	(1,194)	—	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	—	—	—	(14,556)	—	(14,556)
Balances at December 31, 2020	89,945,206	35,354	3,129,384	—	—	—	842	—	(31,885)	(280)	(31,323)
Issuance of Series A convertible preferred stock	22,486,302	10,000	—	—	—	—	—	—	—	—	—
Issuance of Series B convertible preferred stock, net of issuance costs of $348	65,223,679	134,652	—	—	—	—	—	—	—	—	—
Conversion of note payable and accrued interest to Series A convertible preferred stock	5,025,604	2,815	—	—	—	—	—	—	—	—	—
Reclassification of preferred stock tranche rights upon settlement	—	2,592	—	—	—	—	—	—	—	—	—
Conversion of preferred stock to common stock upon initial public offering	(182,680,791)	(185,413)	29,106,831	3	4,835,254	1	185,409	—	—	—	185,413
Issuance of common stock upon initial public offering, net of issuance costs of $3,020	—	—	10,612,500	1	600,000	—	174,249	—	—	—	174,250
Loss on extinguishment of debt	—	—	—	—	—	—	(580)	—	—	—	(580)
Interest on promissory note from related party stockholder	—	—	—	—	—	—	—	—	—	(4)	(4)
Repayment of promissory note from related stockholder party	—	—	—	—	—	—	—	—	—	284	284
Issuance of common stock upon exercise of stock options	—	—	13,460	—	—	—	12	—	—	—	12
Unrealized losses on marketable securities	—	—	—	—	—	—	—	(228)	—	—	(228)
Stock-based compensation expense	—	—	—	—	—	—	3,551	—	—	—	3,551
Net loss	—	—	—	—	—	—	—	—	(46,338)	—	(46,338)
Balances at December 31, 2021	—	$ —	42,862,175	$ 4	5,435,254	$ 1	$363,483	$(228)	$(78,223)	$ —	$285,037

The accompanying notes are an integral part of these consolidated financial statements.

NUVALENT, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,	
	2021	**2020**
Cash flows from operating activities:		
Net loss	$ (46,338)	$ (14,556)
Adjustments to reconcile net loss to net cash used in operating activities:		
Change in fair value of preferred stock tranche rights	635	(2,384)
Stock-based compensation expense	3,551	729
Non-cash interest income on promissory note	(4)	(5)
Net amortization of premiums on marketable securities	215	—
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(251)	(14)
Other assets	(3,196)	—
Accounts payable	1,641	529
Accrued expenses	3,747	752
Net cash used in operating activities	(40,000)	(14,949)
Cash flows from investing activities:		
Purchases of marketable securities	(221,043)	—
Proceeds from sales and maturities of marketable securities	1,015	—
Net cash used in investing activities	(220,028)	—
Cash flows from financing activities:		
Proceeds from issuance of convertible preferred stock and preferred stock tranche rights, net of issuance costs	144,652	22,500
Proceeds from initial public offering, net of underwriting discounts and commissions	177,270	—
Issuance of promissory note to stockholder	—	(250)
Payments of insurance costs financed by a third-party	(976)	—
Proceeds from exercise of stock options	12	15
Proceeds from repayment of promissory note to stockholder	284	—
Payments of initial public offering costs	(3,020)	—
Net cash provided by financing activities	318,222	22,265
Net increase in cash and cash equivalents	58,194	7,316
Cash and cash equivalents at beginning of period	10,332	3,016
Cash and cash equivalents at end of period	$ 68,526	$ 10,332
Supplemental disclosure of noncash financing information:		
Settlement of notes payable and accrued interest for preferred stock	$ 2,235	$ —
Conversion of convertible preferred stock to common stock upon initial public offering	$ 185,413	$ —
Insurance premium financed by a third-party	$ 1,952	$ —
Loss on extinguishment of debt	$ 580	$ —
Settlement of preferred stock tranche rights	$ 2,592	$ (1,194)

The accompanying notes are an integral part of these consolidated financial statements.

NUVALENT, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of Business and Basis of Presentation

Nuvalent, Inc. (the "Company") is a clinical stage biopharmaceutical company focused on creating *precisely* targeted therapies for patients with cancer. The Company was founded in January 2017 as a Delaware corporation. The Company is headquartered in Cambridge, Massachusetts.

The Company is subject to risks similar to those of other pre-commercial stage companies in the biopharmaceutical industry, including dependence on key individuals, the need to develop commercially viable products, competition from other companies, many of whom are larger and better capitalized, the impact of the COVID-19 pandemic and the need to obtain adequate additional financing to fund the development of its product candidates. There can be no assurance that the Company's research and development will be successful, that adequate protection for the Company's intellectual property will be obtained and maintained, that any product candidates will receive required regulatory approval or that approved products, if any, will be commercially viable. Even if the Company's development efforts are successful, it is uncertain when, if ever, the Company will generate significant revenue from the sale of its products.

In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. The Company's operations have not been significantly impacted by the COVID-19 pandemic. However, the Company cannot at this time predict the specific extent, duration, or full impact that the COVID-19 pandemic may have on its financial condition and operations, including its conduct of clinical trials. The impact of the COVID-19 outbreak on the Company's financial performance will depend on future developments, including the duration and spread of the pandemic and related governmental advisories and restrictions. These developments and the impact of COVID-19 on the financial markets and the overall economy are highly uncertain and cannot be predicted. If the financial markets and/or the overall economy are impacted for an extended period, the Company's results may be materially adversely affected.

On July 23, 2021, the Company effected a one-for-5.38213 reverse stock split of its issued and outstanding shares of common stock and a proportional adjustment to the existing conversion ratios for each series of the Company's preferred stock. Accordingly, all share and per share amounts for all periods presented in the accompanying consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect this reverse stock split and adjustment of the preferred stock conversion ratios.

On July 23, 2021, the Company filed an amendment to its amended and restated certificate of incorporation, which effected a recapitalization of the Company's then outstanding common stock to Class A common stock and authorized an additional new class of common stock ("Class B common stock"). The rights of the holders of Class A common stock and Class B common stock are substantially identical, except with respect to voting and conversion. Each share of Class A common stock is entitled to one vote and shares of Class B common stock are non-voting, except as may be required by law. Each share of Class B common stock may be converted at any time into one share of Class A common stock at the option of its holder, subject to the ownership limitations provided for in the Company's amended and restated certificate of incorporation.

On August 2, 2021, the Company completed an initial public offering ("IPO") of its common stock and issued and sold 10,612,500 shares of Class A and 600,000 shares of Class B common stock at a public offering price of $17.00 per share, inclusive of 1,462,500 shares of Class A common stock pursuant to the full exercise of the underwriters' option to purchase additional shares. The Company received net proceeds of approximately $174.3 million after deducting underwriting discounts and commissions and offering costs. In connection with the IPO, the Company's outstanding convertible preferred stock automatically converted into shares of Class A and Class B common stock.

Basis of presentation

The Company's consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to

applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

The consolidated financial statements include the accounts of the Company and its wholly owned subsidiary, Nuvalent Securities Corporation. All intercompany balances and transactions have been eliminated.

Since its inception, the Company has funded its operations primarily with proceeds from sales of preferred stock, issuance of convertible notes (which converted in 2018), debt financing from its investors (which was settled with convertible preferred stock in February 2021), and most recently, with proceeds from the sale of common stock in the IPO completed in August 2021. The Company has incurred recurring losses since inception, including net losses of $46.3 million and $14.6 million for the years ended December 31, 2021 and 2020. As of December 31, 2021, the Company had an accumulated deficit of $78.2 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company believes that its existing cash, cash equivalents and marketable securities will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months from the date of issuance of these consolidated financial statements.

The Company will need to obtain additional funding through public or private equity offerings, debt financings or strategic alliances. 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. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. Arrangements with collaborators or others may require the Company to relinquish rights to certain of its technologies or programs. If the Company is unable to obtain funding, the Company will be required to delay, reduce or eliminate some or all of its research and development programs or the Company may be unable to continue operations. Although management will continue to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations when needed or at all.

2. Summary of Significant Accounting Policies

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, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the valuation of common stock prior to the IPO and preferred stock tranche rights prior to their settlement, the valuation of stock-based awards and the accrual of research and development expenses. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates as there are changes in circumstances, facts and experience. Actual results may differ from those estimates or assumptions.

Concentrations of credit risk and of significant suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and marketable securities. As of December 31, 2021 and 2020, the Company maintained cash, cash equivalents and marketable securities balances in excess of federally insured limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on third-party vendors for the manufacturing of its product candidates. In particular, the Company relies, and expects to continue to rely, on a small number of vendors to manufacture materials and components required for the production of its product candidates. These programs could be adversely affected by a significant interruption in the manufacturing process.

Cash equivalents

The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

Fair value measurements

Certain assets and liabilities are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The Company's cash equivalents and marketable securities are carried at fair value, determined according to the fair value hierarchy described above (see Note 4). The carrying values of the Company's accounts payable and accrued expenses approximate their fair values due to the short-term nature of these liabilities.

Marketable securities

The Company's marketable securities (non-equity instruments) are classified as available-for-sale and are carried at fair value, with the unrealized gains and losses reported as a component of accumulated other comprehensive income (loss) in stockholders' equity (deficit). Realized gains and losses and declines in value determined to be other than temporary are based on the specific identification method and are included as a component of other income (expense), net in the consolidated statements of operations and comprehensive loss.

The Company evaluates its marketable securities with unrealized losses for other-than-temporary impairment. When assessing marketable securities for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary," the Company reduces the investment to fair value through a charge recorded in the consolidated statements of operations. No such adjustments were necessary during the periods presented. The Company classifies its marketable securities with maturities beyond one year as short-term, based on their highly liquid nature and because such marketable securities are available for current operations.

Segment information

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. All of the Company's operations are in the United States.

Research and development costs

Research and development expenses consist of costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, consulting costs, and external costs of vendors engaged to conduct research, preclinical and clinical development activities.

Costs for research and development activities are expensed in the period in which they are incurred. Payments for such activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid expense or accrued research and development expense. Determining the prepaid and accrued balances at the end of any reporting period incorporates certain judgments and estimates by management that are based on information available to the Company including information provided by vendors regarding the progress to completion of specific tasks or costs incurred.

Patent costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

Stock-based compensation

The Company measures stock options with service-based vesting granted to employees, non-employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. The Company measures restricted common stock awards using the difference between the purchase price per share of the award, if any, and the fair value of the Company's common stock at the date of grant. Compensation expense for the awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company uses the straight-line method to record the expense of awards with service-based vesting conditions. The Company accounts for forfeitures of stock-based awards as they occur.

The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Comprehensive income (loss)

Comprehensive income (loss) includes net income (loss) as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. The Company's only element of other comprehensive income (loss) are unrealized gains (losses) on marketable securities.

Net income (loss) per share

Prior to the closing of the IPO, the Company followed the two-class method when computing net income (loss) per share, as the Company had issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Subsequent to the closing of the IPO, basic net income (loss) per common share is computed by dividing the net income (loss) by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) per common share is computed by dividing net income (loss) by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of outstanding stock options and unvested restricted stock units. For periods in which the Company reported a net loss, diluted net loss per common share is the same as basic net loss per common share, since dilutive common shares are not assumed to have been issued if their affect is anti-dilutive.

The Company has two classes of common stock outstanding: Class A common stock and Class B common stock. As more fully described in Note 8, the rights of the holders of Class A and Class B common stock are substantially identical, except with respect to voting and conversion. Each share of Class B common stock is convertible into one share of Class A common stock at the option of the holder at any time, subject to the ownership limitations provided for in the Company's amended and restated certificate of incorporation. The

Company allocates undistributed earnings attributable to common stock between the common stock classes on a one-to-one basis when computing net income (loss) per share. As a result, basic and diluted net income (loss) per share of Class A common stock and share of Class B common stock are equivalent.

The Company excluded the following potential common shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	As of December 31,	
	2021	2020
Convertible preferred stock (as converted to common stock)	—	16,711,823
Unvested restricted common stock	21,129	45,561
Options to purchase common stock	4,909,545	1,433,956
	4,930,674	18,191,340

Income taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to the provision for income taxes. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. Any resulting unrecognized tax benefits are recorded within the provision for income taxes.

Recently issued accounting pronouncements

The Company qualifies as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012 and has elected not to "opt out" of the extended transition related to complying with new or revised accounting standards, which means that when a standard is issued or revised and it has different application dates for public and nonpublic companies, the Company will adopt the new or revised standard at the time nonpublic companies adopt the new or revised standard and will do so until such time that the Company either (i) irrevocably elects to "opt out" of such extended transition period or (ii) no longer qualifies as an emerging growth company.

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842) ("ASU 2016-02"), which requires lessees to recognize most leases on their balance sheet as a right-of-use asset and a lease liability. In general, lease arrangements exceeding a one year term must be recognized as assets and liabilities on the balance sheet. Under ASU 2016-02, a right of use asset and lease obligation is recorded for all leases, whether operating or financing, while the income statement reflects lease expense for operating leases and amortization/interest expense for financing leases. The FASB also issued ASU 2018-10, Codification Improvements to Topic 842 Leases, and ASU 2018-11, Targeted Improvements to Topic 842 Leases, which allows the new lease standard to

be applied as of the adoption date with a cumulative-effect adjustment to the opening balance of retained earnings rather than retroactive restatement of all periods presented. In June 2020, the FASB issued ASU No. 2020-05, which grants a one-year effective-date delay for nonpublic entities to annual reporting periods beginning after December 15, 2021 and to interim periods within fiscal years beginning after December 15, 2022. Early adoption continues to be permitted. Upon adoption of this guidance, the Company will record right-of-use assets and lease liabilities on its consolidated balance sheet for leases it may have as of the adoption date. The Company is assessing the impact that the adoption of this guidance will have on its consolidated financial statements.

In June 2016, the FASB issued ASU No. 2016-13, Financial Instruments – Credit Losses (Topic 326). The new standard adjusts the accounting for assets held at amortized costs basis, including marketable securities accounted for as available for sale, and trade receivables. The standard eliminates the probable initial recognition threshold and requires an entity to reflect its current estimate of all expected credit losses. The allowance for credit losses is a valuation account that is deducted from the amortized cost basis of the financial assets to present the net amount expected to be collected. For public entities except smaller reporting companies, this guidance is effective for annual reporting periods beginning after December 15, 2019 and for interim periods within those years. For nonpublic entities and smaller reporting companies, this guidance was effective for annual reporting periods beginning after December 15, 2021. Early adoption is permitted for all entities. In November 2019, the FASB issued ASU No. 2019-10, which deferred the effective date for nonpublic entities to annual reporting periods beginning after December 15, 2022, including interim periods within those years. Early application continues to be allowed. The Company is currently assessing the impact of the adoption of this guidance on its consolidated financial statements.

3. Marketable Securities

Marketable securities by security type consisted of the following (in thousands):

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper (due within one year)	$ 121,156	$ —	$ (44)	$121,112
Corporate bonds (due within one year)	43,756	—	(60)	43,696
Government securities (due within one year)	4,583	—	(10)	4,573
U.S. treasury securities (due within one year)	10,056	—	(9)	10,047
Corporate bonds (due after one year through two years)	36,218	1	(99)	36,120
Government securities (due after one year through two years)	4,045	—	(8)	4,037
	$ 219,814	$ 1	$ (230)	$219,585

The Company had no marketable securities as of December 31, 2020.

4. Fair Value Measurements

The following tables present the Company's fair value hierarchy for its assets and liabilities, which are measured at fair value on a recurring basis (in thousands):

	Fair Value Measurements at December 31, 2021 Using:			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 67,522	$ —	$ —	$ 67,522
Marketable securities:				
Commercial paper	—	121,112	—	121,112
Corporate bonds	—	79,816	—	79,816
Government securities	—	8,610	—	8,610
U.S. treasury securities	—	10,047	—	10,047
	$ 67,522	$ 219,585	$ —	$ 287,107

	Fair Value Measurements at December 31, 2020 Using:			
	Level 1	Level 2	Level 3	Total
Liabilities:				
Preferred stock tranche rights	$ —	$ —	$ 1,957	$ 1,957

Money market funds were valued by the Company based on quoted market prices, which represent a Level 1 measurement within the fair value hierarchy. Corporate bonds, commercial paper and government securities were valued by the Company using quoted prices in active markets for similar securities, which represent a Level 2 measurement within the fair value hierarchy. During the years ended December 31, 2021 and 2020, there were no transfers in or out of Level 3.

The following table provides a roll-forward of the aggregate fair values of the Company's preferred stock tranche rights, for which fair value was determined by Level 3 inputs (in thousands):

	Preferred Stock Tranche Rights
Fair value at December 31, 2020	$ 1,957
Change in fair value	635
Settlement of preferred stock tranche rights	(2,592)
Fair value at December 31, 2021	$ —

The preferred stock tranche rights represented the fair value of the rights and obligations of the original purchasers of the Series A convertible preferred stock to participate in subsequent closings of Series A convertible preferred stock upon the achievement of certain strategic milestones or as determined by the Series A investors (the "Series A Tranche Rights"), which were fully settled by March 31, 2021. The Series A Tranche Rights met the definition of a freestanding financial instrument as the Series A Tranche Rights were legally detachable and separately exercisable from the Series A convertible preferred stock. The fair value of the Series A Tranche Rights were initially classified as a liability and recorded at fair value and were subject to remeasurement at each reporting date until each Series A Tranche Right was exercised. The fair values of the Series A Tranche Rights were based on significant inputs not observable in the market, which represented a Level 3 measurement within the fair value hierarchy. The Company's valuation of the Series A Tranche Rights utilized a scenario-based valuation analysis, which incorporated assumptions and estimates to value the Series A Tranche Rights and a probability assessment of the achievement of the milestones. The Company assessed these assumptions and estimates at the end of each reporting period as additional information impacting the assumptions were obtained.

The quantitative elements associated with the Company's Level 3 inputs impacting the fair value measurement of the Series A Tranche Rights included the fair value per share of the underlying convertible preferred stock, the expected term of the Series A Tranche Rights, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying convertible preferred stock. The Company determined the fair value per share of the underlying convertible preferred stock by taking into consideration its most recent sales of its convertible preferred stock as well as additional factors that the Company deemed relevant. The Company historically has been a private company and lacks company-specific historical and implied volatility information of its stock. Therefore, it estimated its expected stock volatility based on the historical volatility of a representative group of public companies in the biotechnology industry for the expected terms. The risk-free interest rate was determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the expected terms. The Company estimated a 0% dividend yield based on the expected dividend yield and the fact that the Company has never paid or declared dividends. The Company assessed the probabilities of achieving the milestones related to each tranche upon issuance and at the end of each reporting period. Probabilities ranged from 90.0% to 100.0% and expected terms ranged from 0.2 years to 1.6 years. As of December 31, 2020, the fair value of the Company's Series A convertible preferred stock was $0.53 per share.

The Series A Tranche Rights were exercised in March 2020, August 2020 and February 2021. All Series A Tranche Rights were settled by March 31, 2021.

5. Accrued Expenses

Accrued expenses consisted of the following (in thousands):

	December 31,	
	2021	2020
Accrued employee compensation and benefits	$ 2,730	$ 636
Accrued external research and development expenses	1,757	405
Accrued insurance	976	—
Other	431	130
	$ 5,894	$ 1,171

6. Notes Payable to Related Party

In February 2017, the Company issued $2.0 million of promissory notes (the "Notes") to Deerfield Healthcare Innovations Fund, L.P. and Deerfield Private Design Fund, IV, L.P. (collectively "Deerfield"), an investor in the Company. The Notes accrued interest at a rate of 2.81% per annum, compounded annually, and matured upon the earlier of a change in control event as defined in the Company's charter or five years from issuance. In connection with the issuance of the Notes, the Company entered into a revenue share agreement with Deerfield for contingent payments of a low single digit percentage rate of net sales of commercial product (see Note 11).

In February 2021, the Company issued 5,025,604 shares of Series A convertible preferred stock in full settlement of the Notes and accrued interest. The issuance of the Series A convertible preferred stock was recorded at fair value and as a result, the Company recorded a loss on extinguishment of debt of $0.6 million upon the conversion representing the difference between the carrying value of the Notes and the fair value of the Series A convertible preferred stock. The loss on extinguishment of debt was recognized as additional paid-in capital, a component of stockholders' equity (deficit), due to the related party nature of the Notes.

7. Convertible Preferred Stock

The Company had issued Series A convertible preferred stock (the "Series A") and Series B convertible preferred stock (the "Series B"). The Series A and Series B are collectively referred to as the "Preferred Stock".

Preferred Stock consisted of the following as of December 31, 2020:

	Preferred Stock Authorized	Preferred Stock Issued and Outstanding	Carrying Value	Liquidation Preference	Common Stock Issuable Upon Conversion
			(in thousands)	(in thousands)	
Series A Preferred Stock	112,431,508	89,945,206	$ 35,354	$ 40,000	16,711,823
	112,431,508	89,945,206	$ 35,354	$ 40,000	16,711,823

In April 2021, the Company issued and sold 65,223,679 shares of Series B at a price of $2.0698 per share, for gross proceeds of $135.0 million. There were no tranche rights granted in connection with the Series B issuance and sale. Upon the closing of the IPO, all of the shares of the Company's outstanding Preferred Stock automatically converted into shares of Class A and Class B common stock.

8. Common Stock

On July 23, 2021, the Company filed an amendment to its amended and restated certificate of incorporation, which effected a recapitalization of the Company's then outstanding common stock to Class A common stock and authorized an additional new class of Class B common stock.

The rights of the holders of Class A common stock and Class B common stock are substantially identical, except with respect to voting and conversion. Each share of Class A common stock is entitled to one vote and shares of Class B common stock are non-voting, except as may be required by law. Each share of Class B common stock may be converted at any time into one share of Class A common stock at the option of its holder, subject to the ownership limitations provided for in the Company's amended and restated certificate of incorporation.

Restricted common stock

The Company has outstanding shares of restricted common stock. Shares of unvested restricted common stock may not be sold or transferred by the holder. Vesting may be accelerated upon a change in control, as defined in the restricted stock agreement. If the holders cease to have a business relationship with the Company, the Company may repurchase any unvested shares of common stock held by these individuals at their original purchase price (which was a nominal amount).

9. Stock-Based Compensation

2017 stock option and grant plan

The Company's 2017 Stock Option and Grant Plan (the "2017 Plan") provided for the Company to grant incentive stock options or nonqualified stock options and other equity awards to employees, directors and consultants of the Company. The 2017 Plan was administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting and other restrictions were determined at the discretion of the board of directors, or its committee if so delegated. Upon effectiveness of the Company's 2021 Stock Option and Incentive Plan (the "2021 Plan") in August 2021, the remaining shares available under the 2017 Plan ceased to be available for issuance and no future issuances will be made under the 2017 Plan.

2021 equity incentive plan

On July 23, 2021, the Company's board of directors adopted and its stockholders approved the 2021 Plan, which became effective on July 28, 2021. The 2021 Plan provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units, unrestricted stock awards, cash-based awards and dividend equivalent rights. The number of Class A shares of common stock initially reserved for issuance under the 2021 Plan is 5,866,004, which shall be cumulatively increased on January 1, 2022 and each January 1 thereafter by 5.0% of the number of shares of the Company's Class A and Class B common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by the Company's board of directors or compensation committee of the board of

directors. The shares of Class A common stock underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of stock, expire or are otherwise terminated (other than by exercise) under the 2021 Plan and the 2017 Plan will be added back to the shares of Class A common stock available under the 2021 Plan. As of December 31, 2021, 5,267,107 shares remained available for future issuance under the 2021 Plan. The number of authorized shares reserved for issuance was increased by 2,414,871 shares effective as of January 1, 2022, in accordance with the provisions of the 2021 Plan described above.

2021 employee stock purchase plan

On July 23, 2021, the Company's board of directors adopted and its stockholders approved the 2021 Employee Stock Purchase Plan (the "ESPP"), which became effective on July 28, 2021. A total of 473,064 shares of Class A common stock were reserved for issuance under this plan. In addition, the number of shares of Class A common stock that may be issued under the ESPP will automatically increase on January 1, 2022, and each January thereafter through January 1, 2031, by the least of (i) 473,064 shares of Class A common stock, (ii) 1% of the number of shares of the Company's Class A and Class B common stock outstanding on the immediately preceding December 31st or (iii) such lesser number of shares as determined by the administrator of the Company's ESPP. As of December 31, 2021, no offering periods have commenced under the ESPP. The number of authorized shares reserved for issuance was increased by 473,064 shares effective as of January 1, 2022, in accordance with the provisions of the ESPP described above.

Stock option valuation

The fair value of stock option grants is estimated using the Black-Scholes option-pricing model. The Company historically has been a private company and lacks company-specific historical and implied volatility information. Therefore, it estimates its expected stock volatility based on the historical volatility of a publicly traded set of peer companies and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the grant-date fair value of stock options granted:

	Year Ended December 31,	
	2021	2020
Risk-free interest rate	0.8%	0.4%
Expected volatility	79.8%	81.2%
Expected dividend yield	—	—
Expected term (in years)	6.1	6.3

The following table summarizes the Company's option activity since December 31, 2020:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2020	1,433,956	$ 0.69	9.43	$ 255
Granted	3,535,047	8.68		
Exercised	(13,460)	0.87		
Forfeited	(45,998)	1.65		
Outstanding as of December 31, 2021	4,909,545	$ 6.44	9.09	$ 62,702
Vested and expected to vest as of December 31, 2021	4,909,545	$ 6.44	9.09	$ 62,702
Options exercisable as of December 31, 2021	670,299	$ 2.13	8.42	$ 11,330

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2021 and 2020 was $0.3 million and less than $0.1 million, respectively.

The weighted average grant-date fair value of stock options granted during the years ended December 31, 2021 and 2020 was $5.87 per share and $0.49 per share, respectively.

Restricted common stock

During 2017, the Company issued and sold 1,300,600 shares of restricted common stock at par value to the scientific founder of the Company (the "Original Shares"). The Original Shares vested as to 25% of the total on the date of grant and the remaining 75% were vested over a period of three years.

The Company has also issued shares of restricted stock that generally vest over four years.

The following table summarizes the Company's restricted common stock activity since the year ended December 31, 2020 (in thousands, except share amounts):

	Shares	Weighted Average Grant Date Fair Value
Unvested restricted common stock as of December 31, 2020	45,561	$ 30
Issued	—	$ —
Vested	(24,432)	$ 8
Forfeited	—	$ —
Unvested restricted common stock as of December 31, 2021	21,129	$ 22

The aggregate fair value of restricted stock that vested during the year ended December 31, 2021 was less than $0.1 million. The aggregate fair value of restricted stock that vested during the year ended December 31, 2020 was $0.1 million.

Stock-based compensation

The Company recorded stock-based compensation expense related to common stock options and restricted common stock in the following expense categories of its consolidated statements of operations and comprehensive loss (in thousands):

	Year Ended December 31,	
	2021	2020
Research and development expenses	$ 1,349	$ 657
General and administrative expenses	2,202	72
	$ 3,551	$ 729

As of December 31, 2021, total unrecognized compensation cost related to common stock options and unvested restricted stock was $17.7 million, which is expected to be recognized over a weighted average period of 2.97 years.

10. Income Taxes

During the years ended December 31, 2021 and 2020, the Company recorded no income tax benefits for the net operating losses incurred or for the research and development tax credits generated in each year, due to its uncertainty of realizing a benefit from those items.

All of the Company's operating losses since inception have been generated in the United States.

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2021	2020
Federal statutory income tax rate	21.0%	21.0%
State income taxes, net of federal benefit	6.2	7.2
Permanent differences	—	(1.9)
Tax credits generated	4.1	4.6
Change in deferred tax asset valuation allowance	(29.5)	(34.2)
Series A tranche rights change in fair value	(1.1)	3.4
Stock-based compensation	(0.7)	(0.1)
Effective income tax rate	(0.0)%	(0.0)%

Net deferred tax assets consisted of the following (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 19,951	$ 8,300
Research and development tax credit carryforwards	2,175	497
Intangible assets	74	821
Stock-based compensation	499	—
Other	705	165
Total deferred tax assets	23,404	9,783
Valuation allowance	(23,400)	(9,780)
Net deferred tax assets	4	3
Deferred tax liabilities:		
Other	$ (4)	$ (3)
Total deferred tax liabilities	(4)	(3)
Net deferred tax assets	$ —	$ —

As of December 31, 2021, the Company had U.S. federal and state net operating loss carryforwards of $73.2 million and $72.5 million, respectively, which may be available to offset future taxable income. The federal net operating losses include $1.1 million which expire in 2037 and $72.1 million which carryforward indefinitely, but may only be used to offset 80% of annual taxable income. The state net operating losses expire at various dates beginning in 2037. As of December 31, 2021, the Company also had federal and state research and development tax credit carryforwards of $1.6 million and $0.7 million, respectively, which may be available to offset future tax liabilities and expire at various dates beginning in 2033.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income or tax liabilities. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382. Any limitation may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before utilization. Further, until a study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products that would generate revenue from product sales and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2021 and 2020. Management reevaluates the positive and negative evidence at each reporting period.

The valuation allowance increased during the years ended December 31, 2021 and 2020, primarily as a result of the increase in net operating loss carryforwards. The changes in the valuation allowance for the years ended December 31, 2021 and 2020 were as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Valuation allowance as of beginning of year	$ 9,780	$ 4,796
Increases recorded to income tax provision	13,620	4,984
Valuation allowance as of end of year	$ 23,400	$ 9,780

As of December 31, 2021 and 2020, the Company had not recorded any amounts for unrecognized tax benefits. The Company files income tax returns in the U.S. and Massachusetts, as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. The Company is open to future tax examination under statute from 2018 to the present.

11. Commitments and Contingencies

Revenue share

The Company has revenue sharing agreements with Deerfield and the Company's scientific founder to pay each of Deerfield and the scientific founder a low single digit percentage rate of net sales of certain commercial products. The payment obligation expires on the later of 12 years from the first commercial sale in a country or the expiration of the last-to-expire patent in that country for both Deerfield and the Company's scientific founder. The Company accounts for this liability at fair value with changes recognized in the statements of operations and comprehensive loss. Given the early-stage nature of the underlying technology and inherent risks associated with obtaining regulatory approval and achieving commercialization, the Company ascribed no value to either of the revenue sharing agreements at inception and at December 31, 2021 and 2020. The Company currently does not have any net sales and as a result has paid no amounts under these obligations nor has the Company accrued any liability as of December 31, 2021 and 2020.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, contract research organizations, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. The Company has not incurred any material costs as a result of such indemnifications and is not currently aware of any indemnification claims.

12. Defined Contribution Plan

The Company has a 401(k) defined contribution plan (the "401(k) Plan") for its employees. Eligible employees may make pretax contributions to the 401(k) Plan up to statutory limits. There was no discretionary match made under the 401(k) Plan as of December 31, 2021 and 2020. In September 2021, the Company adopted a match program for employee contributions to the 401(k) Plan up to a maximum of six percent of the employee's salary for the year ended December 31, 2022.

13. Related Parties

The Company had issued certain promissory notes to Deerfield, an investor in the Company. In February 2021, the promissory notes and accrued interest were converted to Series A (see Note 6).

The Company is obligated to pay low single digit percentage rates of net sales of certain commercial products to Deerfield and its scientific founder. As of December 31, 2021 and 2020, no products have been commercialized and no amounts have been paid or become due (see Note 11).

In February 2017, the Company entered into a three-year consulting agreement with the scientific founder of the Company who is also a board member and a stockholder. The consulting agreement between the scientific founder and the Company continues at will. During the years ended December 31, 2021 and 2020, the Company paid the scientific founder $0.3 million and $0.2 million, respectively. As of December 31, 2021 and 2020, the Company had less than $0.1 million and no accounts payable, respectively, to the scientific founder.

In June 2020, the Company loaned $0.3 million to the scientific founder of the Company who is also a board member and a stockholder of the Company related to the issuance of common stock (see Note 9) pursuant to a promissory note. The promissory note provided that the unpaid principal amount of the loan bore interest at 2.86% annually, and interest was payable annually or was converted to principal at the maturity date. The promissory note provided that the maturity date of the promissory note would occur on the earliest to occur of (i) June 11, 2024, (ii) 60 calendar days following the date of termination of services of the stockholder, and (iii) immediately prior to an initial filing of a registration statement by the Company. The promissory note was fully repaid and cancelled in July 2021.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our President and Chief Executive Officer and our Chief Financial Officer (our principal executive officer and principal financial and accounting officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. 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 the evaluation of our disclosure controls and procedures as of December 31, 2021, our President and Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

This annual report does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of the Company's independent registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

Changes in Internal Control over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2021, that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information concerning our executive officers is set forth under the heading Information about our Executive Officers in Item 1 of this Annual Report on Form 10-K. The remaining information required by this Item 10 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

1. Financial Statements

For a list of the financial statements included herein, see Index to the Consolidated Financial Statements on page 158 of this Annual Report, incorporated into this Item by reference.

2. Financial Statement Schedules

Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

3. Exhibits

The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report are listed in the Exhibit Index immediately preceding the signature page of this Annual Report. The exhibits listed in the Exhibit Index are incorporated by reference herein.

ITEM 16. FORM 10-K SUMMARY

None.

Item 6. Exhibits.

Exhibit Number	Description of Exhibit	Form	File No.	Exhibit	Filing Date	Filed Herewith
3.1	Third Amended and Restated Certificate of Incorporation of the Registrant	8-K	001-40671	3.1	8/2/2021	
3.2	Amended and Restated Bylaws of the Registrant	8-K	001-40671	3.2	8/2/2021	
4.1	Specimen Class A Common Stock Certificate	S-1	333-257730	4.1	7/7/2021	
4.2	Specimen Class B Common Stock Certificate	S-1	333-257730	4.2	7/7/2021	
4.3	Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, effective as of April 30, 2021	S-1	333-257730	4.3	7/7/2021	
4.4	Description of Securities Registered Under Section 12 of the Exchange Act					X
10.1#	2021 Stock Option and Incentive Plan and forms of award agreements thereunder	S-1/A	333-257730	10.2	7/26/2021	
10.2#	2021 Employee Stock Purchase Plan	S-1/A	333-257730	10.3	7/26/2021	
10.3#	Form of Indemnification Agreement between the Registrant and each of its directors	S-1	333-257730	10.4	7/7/2021	

Exhibit Number	Description of Exhibit	Form	File No.	Exhibit	Filing Date	Filed Herewith
10.4#	Form of Indemnification Agreement between the Registrant and each of its executive officers	S-1	333-257730	10.5	7/7/2021	
10.5#	Senior Executive Cash Incentive Bonus Plan	S-1	333-257730	10.6	7/7/2021	
10.6#α	Form of Executive Employment Agreement	S-1	333-257730	10.7	7/7/2021	
10.7#	Non-Employee Director Compensation Policy					X
10.8#	Employment Agreement, by and between the Registrant and James R. Porter, effective August 2, 2021	S-1	333-257730	10.9	7/7/2021	
10.9†	Amended and Restated Revenue Sharing Agreement, by and between the Registrant and Matthew Shair, effective as of February 2, 2017	S-1	333-257730	10.11	7/7/2021	
10.10†	Amended and Restated Revenue Sharing Agreement, by and between the Registrant, Deerfield Healthcare Innovations Fund, L.P. and Deerfield Private Design Fund, IV, L.P., effective as of February 2, 2017	S-1	333-257730	10.12	7/7/2021	
21.1	Subsidiaries of the Registrant					X
23.1	Consent of KPMG LLP, 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

Exhibit Number	Description of Exhibit	Form	File No.	Exhibit	Filing Date	Filed Herewith
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document					
101.SCH	Inline XBRL Taxonomy Extension Schema Document					
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document					
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)					

\# Indicates a management contract or any compensatory plan, contract or arrangement.

α Nuvalent, Inc. has entered into an Executive Employment Agreement with each of Alexandra Balcom, Deborah Miller, Darlene Noci and Christopher D. Turner.

† Portions of this exhibit (indicated by asterisks) have been omitted in accordance with Item 601(b)(10) of Regulation S-K.

\+ The certifications furnished in Exhibits 32.1 and 32.2 hereto are deemed to be furnished with this Annual Report on Form 10-K and will not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

NUVALENT, INC.

Date: March 29, 2022

By: /s/ James R. Porter
James R. Porter, Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ James R. Porter James R. Porter, Ph.D.	President, Chief Executive Officer and Director (Principal Executive Officer)	March 29, 2022
/s/ Alexandra Balcom Alexandra Balcom	Chief Financial Officer (Principal Financial and Accounting Officer)	March 29, 2022
/s/ Emily Drabant Conley Emily Drabant Conley, Ph.D.	Director	March 29, 2022
/s/ D. Gary Gilliland D. Gary Gilliland, M.D., Ph.D.	Director	March 29, 2022
/s/ Andrew A. F. Hack Andrew A. F. Hack, M.D., Ph.D.	Director	March 29, 2022
/s/ Robert Jackson Robert Jackson, M.D.	Director	March 29, 2022
/s/ Joseph Pearlberg Joseph Pearlberg, M.D., Ph.D.	Director	March 29, 2022
/s/ Matthew Shair Matthew Shair, Ph.D.	Director	March 29, 2022
/s/ Sapna Srivastava Sapna Srivastava	Director	March 29, 2022
/s/ Cameron A. Wheeler Cameron A. Wheeler, Ph.D.	Director	March 29, 2022

LEADERSHIP

Ruth Adams
Vice President, Clinical Operations

Alex Balcom, MBA, CPA
Chief Financial Officer

Joshua Horan, PhD
Vice President, Chemistry

Benjamin Lane, PhD
Vice President,
Pharmaceutical Development

Jessie Lin
Vice President, Corporate Strategy
& Portfolio Management

Matthew Metivier
Vice President, Human Resources

Deb Miller, PhD, JD
Chief Legal Officer

Darlene Noci, ALM
Senior Vice President, Product
Development & Regulatory Affairs

Henry Pelish, PhD
Vice President, Biology

James Porter, PhD
Chief Executive Officer

John Soglia, PhD
Vice President,
Translational Development

Christopher Turner, MD
Chief Medical Officer

BOARD OF DIRECTORS

Emily Drabant Conley, PhD
Chief Executive Officer,
Federation Bio

Gary Gilliland, MD, PhD
Former President and Director of the
Fred Hutchinson Cancer Research Center

Andrew A.F. Hack, MD, PhD
Managing Director,
Bain Capital Life Sciences

Robert Jackson, MD
Former Partner and Chief Science
Officer, Deerfield Management

Joseph Pearlberg, MD, PhD
VP of Scientific Affairs,
Deerfield Management

James Porter, PhD
Chief Executive Officer, Nuvalent

Anna Protopapas
President and Chief Executive Officer,
Mersana Therapeutics

Matthew D. Shair, PhD
Founder, Head Scientific Advisor,
Nuvalent
Professor of Chemistry and Chemical
Biology, Harvard University

Sapna Srivastava, PhD
Former Interim Chief Financial Officer,
eGenesis Bio

Cameron Wheeler, PhD
Partner, Deerfield Management

Annual Meeting of Stockholders

The 2022 annual meeting of stockholders will be held on Thursday, June 16, 2022 at 1:00 p.m. Eastern Time online at www.virtualshareholdermeeting.com/NUVL2022

Stock Listing

Nasdaq: NUVL

Independent Auditors

KPMG LLP

SEC Form 10-K

A copy of Nuvalent's Form 10-K filed with the Securities and Exchange Commission is available free of charge from Nuvalent's Investor Relations Department by calling (857) 357-7000, emailing ir@nuvalent.com or sending a written request to: Investor Relations, Nuvalent, One Broadway 14th Floor, Cambridge, MA 02142.

Transfer Agent

The transfer agent is responsible, among other things, for handling stockholder questions regarding stock ownership, address changes, including duplicate mailings, and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address: Computershare Trust Company, N.A., Meidinger Tower, 462 South 4th Street, Louisville, KY 40202, www-us.computershare.com/contactus

Cautionary Note Regarding Forward-Looking Statements

This annual report contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding Nuvalent's strategy, business plans, and focus; the clinical development programs for NVL-520, NVL-655, ALK IXDN compound resistance mutations and HER2 Exon 20 insertions and the timing thereof; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 study and the timing thereof; the design and initiation of the ALKOVE-1 Phase 1/2 study and the timing thereof; the potential of Nuvalent's pipeline programs, including NVL-520 and NVL-655; Nuvalent's research and development programs for the treatment of cancer; risks and uncertainties associated with drug development; and capital allocation. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "aim," "goal," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" or the negative of these terms and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. You should not place undue reliance on these statements or the scientific data presented.

Any forward-looking statements in this annual report are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties, and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this annual report, including, without limitation: risks that Nuvalent may not fully enroll the ARROS-1 study or it will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during clinical trials; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; risks that Nuvalent may not be able to nominate drug candidates from its HER2 Exon 20 and ALK IXDN programs; the direct or indirect impact of the COVID-19 pandemic on the timing and anticipated timing and results of Nuvalent's clinical trials, strategy, and future operations, including the global ARROS-1 study and the planned initiation of the ALKOVE-1 Phase 1/2 study; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; and obtaining, maintaining, and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2021, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Nuvalent's views only as of the date of this annual report and should not be relied upon as representing its views as of any subsequent date. Nuvalent explicitly disclaims any obligation to update any forward-looking statements.

Nuvalent

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