blueprint™ MEDICINES

2022

Annual Report

KEEPING PATIENTS IN FOCUS

NASDAQ: **BPMC**

Cyndi N.
Living with SM

Kate Haviland
President & Chief Executive Officer

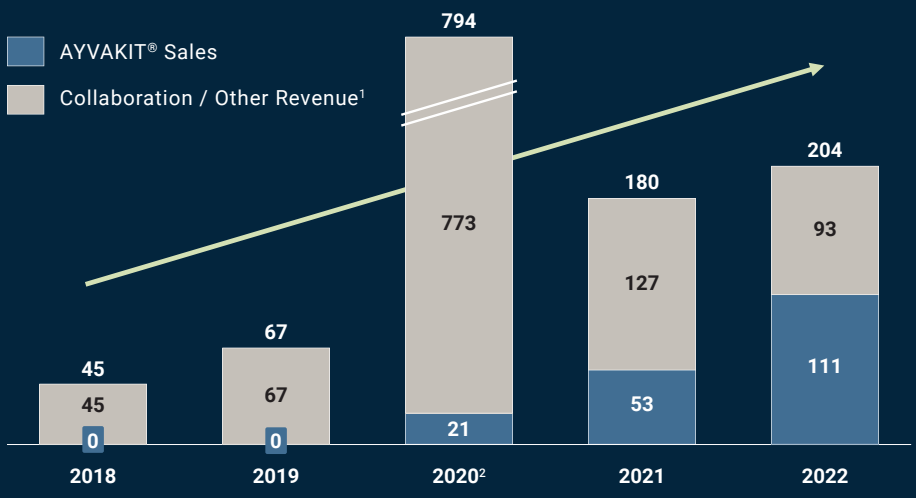
> In 2022, we achieved important progress toward our **2027 Blueprint for Precision at Scale**, a five-year growth strategy to bring transformative precision medicines to large populations of patients with cancer and blood disorders.

Dear Stockholders:

In 2022, we made important advancements toward our 2027 Blueprint for Precision at Scale, a five-year growth strategy to bring transformative precision therapies to large populations of patients with cancer and blood disorders.

Building on more than a decade of research and development success, we have built a portfolio of commercial medicines and strong organizational capabilities and global infrastructure. Our five-year strategy aims to achieve scale across three focus areas: mast cell disorders including systemic mastocytosis, or SM, EGFR-driven lung cancer, and CDK2-vulnerable breast and other cancers. As we achieve our goal of doubling our commercial portfolio and research and development productivity in this timeframe, we will dramatically expand our impact on patients globally and drive exceptional long-term financial performance.

BLUEPRINT MEDICINES NET REVENUE ($M)



[1] Includes GAVRETO® (pralsetinib) sales booked as revenue in 2020 and 2021.
[2] Includes Roche collaboration payments.

In 2022, we more than doubled our commercial

revenue by establishing AYVAKIT® (avapritinib) as the standard of care for advanced SM in the U.S. and initiating the commercial launch of AYVAKYT® (avapritinib) for advanced SM in the EU.

In 2023, we expect AYVAKIT net product revenues of $130 million to $140 million for currently approved indications, and anticipate additional product revenue resulting from a potential indication expansion in indolent SM. With more than $1 billion in cash and investments entering 2023 and continued strong product revenue growth anticipated over the next several years, we have an exceptionally strong financial foundation to achieve our ambitious vision.

Today, we are at the precipice of

significant near-term growth in SM due to the compelling efficacy and safety results we saw in 2022 from the registration-directed PIONEER clinical trial of AYVAKIT in patients with indolent SM, an opportunity we estimate to be 15-fold larger than AYVAKIT's approved advanced SM indication, if approved. In total, we believe SM represents more than a $1.5 billion global peak revenue opportunity.

In the PIONEER trial, AYVAKIT achieved the primary and all key secondary endpoints, demonstrating statistically significant and clinically meaningful impact on measures of mast cell burden, disease symptoms, and quality of life, along with a safety profile favorable to placebo plus best supportive care.

As we finalize preparations for a potential U.S. launch of AYVAKIT in indolent SM, we are uniquely positioned to deliver the first and only disease-modifying therapy to patients living with this disease.

We are building the foundation

for additional blockbuster opportunities in lung and breast cancer with a research and development strategy focused on designing and developing potent and selective small molecule precision therapies with first- or best-in-class potential. Today, we are making important progress generating early clinical data for multiple therapeutic candidates for EGFR-driven lung cancer and CDK2-vulnerable breast cancer, and these results are informing development strategies to create value for patients and our shareholders.

We are purposefully evolving

our corporate governance as our business continues to mature and we position Blueprint Medicines for growth, with an approach that is responsive to shareholder feedback and consistent with our peers in the biopharmaceutical industry.

We recently welcomed two new independent directors, Habib Dable and Dr. John Tsai, which also advanced our commitment to ensuring our board is comprised of directors who have the industry experience and expertise that directly maps to our business strategy and enables them to think ahead of the current state of the business. Our board is comprised of exceptionally competent leaders committed to the long-term mission of the business. In addition to diversity in expertise, our board represents strong demographic diversity with five of ten directors (50 percent) being diverse by gender or race/ethnicity today. All of our board committees are chaired and composed solely of independent directors and the leadership roles on all of our board committees are held by diverse board members either by gender or race/ethnicity.

We have also evolved multiple aspects of our governance having implemented an over-boarding policy, added proxy access provisions in our bylaws, adopted an average tenure goal of ten years or less for independent directors and, beginning in 2023, introduced performance share unit awards to our equity incentive program, to further align the interests of our executive officers with our shareholders.

The future for Blueprint Medicines

is bright because we have the people, portfolio, and capabilities to successfully execute on our strategy. Today, Blueprint Medicines is a successful global commercial-stage biopharmaceutical company with growing product revenue and a pipeline of promising programs. We have a clear strategic direction to achieve our goals and a culture of excellence intentionally built with participation at all levels. Finally, we have an impressive board of directors and a passionate team of employees and partners who are deeply committed to our vision for changing patient outcomes.

On behalf of our board of directors and employees, thank you for your continued support and investment in Blueprint Medicines.

Sincerely,

Kate Haviland
President, Chief Executive Officer, and Director
On Behalf of the Board of Directors

Cambridge, Massachusetts
April 28, 2023

SM patients sharing creative expression of their disease

In 2022, Blueprint Medicines invited those impacted by systemic mastocytosis (SM) or other mast cell disorders to share a creative expression of their disease. The resulting artistic submissions illustrate unique experiences with a disease that is associated with significant symptom burden and isolation, which can lead to poor physical and physiological quality of life.

Systemic Mastocytosis (SM) is a rare disease where the body's mast cells (that regulate allergic reactions) are over-produced and overactive. People living with SM experience debilitating symptoms that can involve multiple body symptoms such as skin lesions, gastrointestinal issues, brain fog and fatigue and even life-threatening anaphylaxis. This has significant impact on their daily life: they may need to isolate themselves to protect against triggers for their symptoms. For more than a decade, Blueprint has partnered with the SM community to better understand patient burden, accelerate diagnosis and improve treatment.

Popsicle City By Diana

Summer at the Pond by Pamela

> I have suffered from systemic mastocytosis for nearly 10 years and because so many things in my life trigger an allergic reaction, I don't leave home often. My backyard has become my sanctuary. I use photography as a creative outlet and the dragonflies that frequent our pond are my favorite subjects.

Navigating Mastocytosis By Rachael

> This art illustrates what it has felt like navigating mastocytosis for me. It's a lot of feeling like you are running in circles trying to get your doctors to care, to navigate our country's medical system, and having to ask every person you need to share space with to accommodate you. Fragrances are by far my biggest trigger and despite spending a considerable amount of time educating people and advocating for increased accessibilities, it still often feels like I'm just yelling into a void.

The Abusive Nature of Mast Cell Disease and the Isolation of Fragrance Triggers of Anaphylaxis

by Eliza

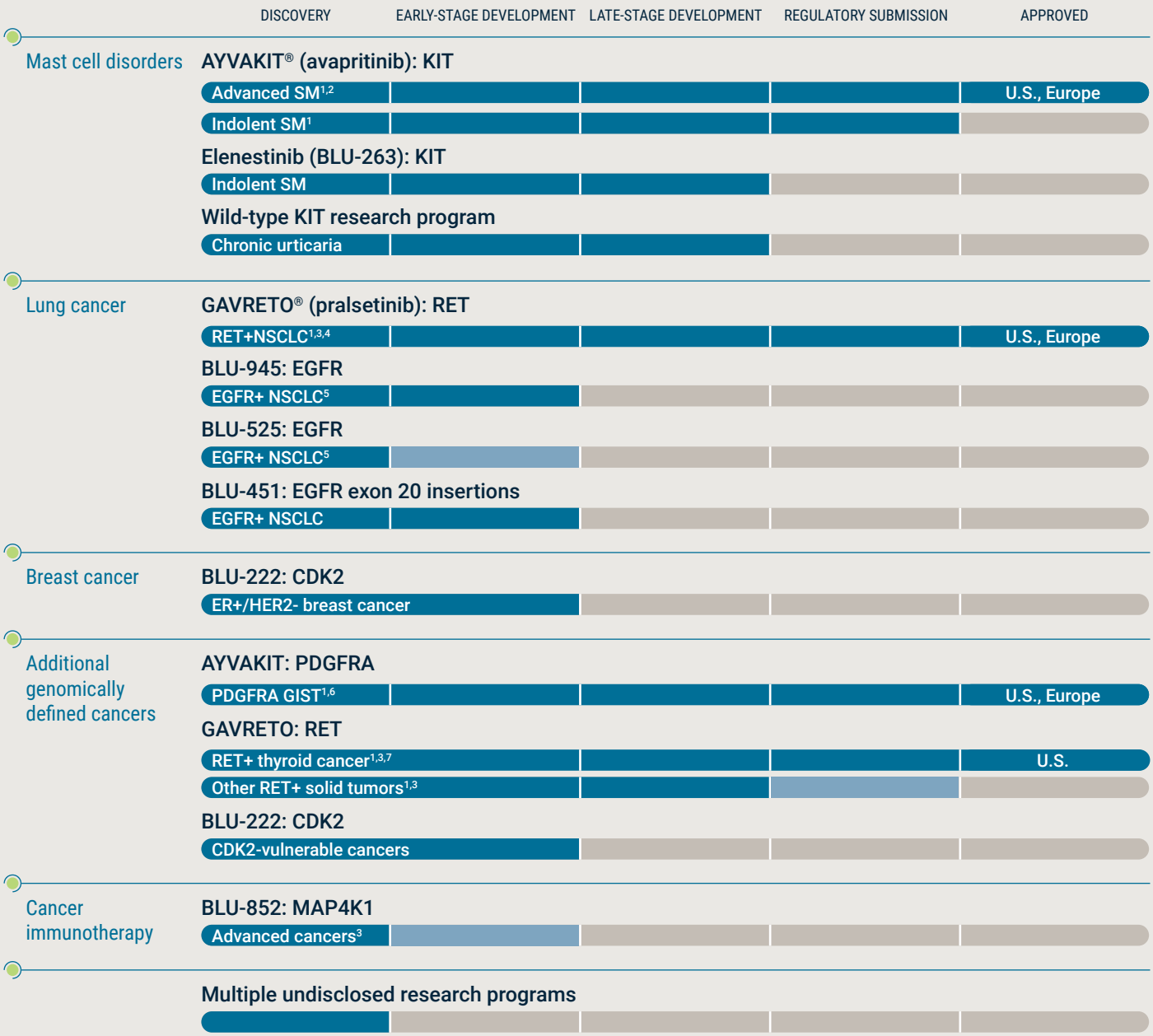
July 10, 2022

I snuck out of the house
breathed without your permission
and felt the back of your hand across my red face
the heat on my cheeks lasted into the nausea
and the fear that came over me drove me inside
running toward the house
hoping that
you would just cut me some slack this time.

I begged you to help me
as drops of fear and blood flowed out
clutching the autoinjector that could bring me back to life
as you poisoned me, pained me, and grabbed for my throat
I swallowed down meds to make it more bearable
till your hatred passed
praying for
the option to just sleep it away.

Toxic relationship
I cannot escape you
I am trying to love you in the midst of this
I keep hoping that you will change and I'll be free
to do all of the things that other people do
no longer shamed by the
abuse inflicted
on me by my own body.

Blueprint Medicines' rapidly expanding portfolio highlights our precision therapy leadership



Ongoing or completed Planned

Updated as of February 16, 2023

1. CStone Pharmaceuticals has exclusive rights to develop and commercialize avapritinib and pralsetinib in Greater China. 2. Approved in the U.S. for adults with advanced SM, including aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN) and mast cell leukemia (MCL). Approved in Europe (AYVAKYT®) for adults with ASM, SM-AHN or MCL, after at least one systemic therapy. 3. In collaboration with Roche. 4. Received U.S. accelerated approval for adults with metastatic RET fusion-positive NSCLC. Received conditional marketing authorization in Europe for adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor. 5. Zai Lab has exclusive rights to develop and commercialize BLU-945 and BLU-525 in Greater China. 6. Approved in the U.S. for adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. Approved in Europe (AYVAKYT®) for adults with unresectable or metastatic GIST harboring the PDGFRA D842V mutation. 7. Received U.S. accelerated approval for advanced or metastatic RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 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: 001-37359

BLUEPRINT MEDICINES CORPORATION
(Exact name of registrant as specified in its charter)

Delaware	**26-3632015**
(State or other jurisdiction of incorporation or organization)	*(IRS Employer Identification No.)*
45 Sidney Street Cambridge, MA	**02139**
(Address of principal executive offices)	*(Zip Code)*

Registrant's telephone number, including area code: **(617) 374-7580**

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

Title of Class	*Trading Symbols*	*Name of Exchange on Which Registered*
Common Stock, par value $0.001 per share	**BPMC**	**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 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. Yes ☑ No ☐

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

As of June 30, 2021, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last reported sales price for the registrant's common stock, par value $0.001 per share, on the Nasdaq Global Select Market on such date, was approximately $5,150,459,010.

Number of shares of the registrant's common stock, par value $0.001 per share, outstanding on February 15, 2022: 59,203,486

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2022 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A within 120 days after the end of the registrant's fiscal year ended December 31, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K.

Auditor Firm Id: 42 Auditor Name: Ernst & Young LLP Auditor Location: Boston, Massachusetts, United States

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Unless otherwise stated, all references to "us," "our," "Blueprint," "Blueprint Medicines," "we," the "Company" and similar designations in this Annual Report on Form 10-K refer to Blueprint Medicines Corporation and its consolidated subsidiaries. Blueprint Medicines, AYVAKIT®, AYVAKYT®, GAVRETO® and associated logos are trademarks of Blueprint Medicines Corporation. Other brands, names and trademarks contained in this Annual Report on Form 10-K are the property of their respective owners.

RISK FACTOR SUMMARY

Below is a summary of the material risks to our business, operations and the investment in our common stock. This summary does not address all of the risks that we face. Risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K in its entirety before making investment decisions regarding our common stock.

- We have limited experience as a commercial company and the marketing and sale of AYVAKIT® (avapritinib) (marketed in Europe under the brand name AYVAKYT®), GAVRETO® (pralsetinib) or any future approved drugs may be unsuccessful or less successful than anticipated.
- The commercial success of our current and future drugs will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.
- If we are unable to establish additional commercial capabilities and infrastructure, we may be unable to generate sufficient revenue to sustain our business.
- If the market opportunities for our approved drugs or drug candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability will be adversely affected.
- We face substantial competition, which may result in others commercializing, developing or discovering drugs before or more successfully than we do.
- Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any of our approved drugs or drug candidates that we may develop.
- If we are unable to advance our drug candidates to clinical development, obtain regulatory approval for our drug candidates, including for avapritinib and pralsetinib for additional indications or in additional geographies, and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed.
- If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.
- If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our drug candidates and, if applicable, for any related companion diagnostic tests, we will not be able to commercialize, or may be delayed in commercializing, such drug candidates, and our ability to generate revenue will be materially impaired.
- Our drugs and drug candidates may cause undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, result in restrictive distribution or result in significant negative consequences following marketing approval, if any.
- We may not be successful in our efforts to expand our pipeline of drug candidates.
- We are required to comply with comprehensive and ongoing regulatory requirements for any of our current or future approved drugs, including conducting confirmatory clinical trials for any drug that

receives accelerated approval. In addition, our current or future approved drugs could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drugs.

- We are a precision therapy company with a limited operating history. We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.

- We have entered into collaborations and licenses with our partners for the development and commercialization of several of our drugs and drug candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these drugs and drug candidates.

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

- We contract with third parties for the manufacture of our approved drugs and drug candidates, including for preclinical, clinical and commercial supply. This reliance on third parties increases the risk that we will not have sufficient quantities of our approved drugs or drug candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

- If we are unable to adequately protect our proprietary technology or obtain and maintain patent protection for our technology and drugs or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and drugs similar or identical to ours, and our ability to successfully commercialize our technology and drugs may be impaired.

- Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

- Our business, results of operations and future growth prospects could be materially and adversely affected by the ongoing COVID-19 pandemic.

- We may acquire or in-license businesses, technologies or platforms, approved drugs, drug candidates or discovery-stage programs, or form strategic alliances, collaborations or partnerships, in the future, and we may not realize the benefits of such acquisitions, in-licenses, alliances, collaborations or partnerships.

- The price of our common stock has been and may in the future be volatile and fluctuate substantially.

FORWARD-LOOKING STATEMENTS

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

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

- the timing or likelihood of regulatory actions, filings and approvals for our current and future drug candidates, including our ability to obtain marketing approval for avapritinib and pralsetinib for additional indications or in additional geographies;
- our ability and plans in continuing to build out our commercial infrastructure and successfully launching, marketing and selling AYVAKIT (avapritinib) (marketed in Europe under the brand name AYVAKYT), GAVRETO (pralsetinib) and any current and future drug candidates for which we receive marketing approval;
- the rate and degree of market acceptance of AYVAKIT/AYVAKYT, GAVRETO and any current and future drug candidates for which we receive marketing approval;
- the pricing and reimbursement of AYVAKIT/AYVAKYT, GAVRETO and any current and future drug candidates for which we receive marketing approval;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, including our ongoing clinical trials and any planned clinical trials for our current and future drug candidates and research and development programs;
- our ability to advance drug candidates into, and successfully complete, clinical trials;
- our ability to successfully develop manufacturing processes for any of our current and future drugs or drug candidates and to secure manufacturing, packaging and labeling arrangements for development activities and commercial production;
- the implementation of our business model and strategic plans for our business, drugs, drug candidates, platform and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our current and future drugs, drug candidates and technology;
- the potential benefits of our collaboration with F. Hoffmann-La Roche Ltd and Genentech, Inc. to develop and commercialize pralsetinib globally (excluding Greater China), our cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., our collaboration with CStone Pharmaceuticals to develop and commercialize avapritinib, pralsetinib and fisogatinib in Greater China, and our collaboration with Zai Lab to develop and commercialize BLU-701 and BLU-945 as inhibitors of epidermal growth factor receptor (EGFR), as well as our ability to maintain these collaborations and establish additional strategic collaborations;
- the potential benefits of our exclusive license agreement with Clementia Pharmaceuticals, Inc. to develop and commercialize BLU-782 for fibrodysplasia ossificans progressiva;
- the development of companion diagnostic tests for our current or future drugs or drug candidates;

- our financial performance, estimates of our revenues, expenses and capital requirements and our needs for future financing, including our ability to achieve a self-sustainable financial profile;

- developments relating to our competitors and our industry;

- the actual or potential benefits of designations granted by the U.S. Food and Drug Administration, or FDA, such as orphan drug, fast track and breakthrough therapy designation or priority review; and

- the impact and scope of the ongoing COVID-19 pandemic on our business, operations, strategy, goals and anticipated milestones, including our ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, and the launch, marketing, sale and commercial supply of AYVAKIT/AYVAKYT, GAVRETO and any current or future drug candidates for which we receive marketing approval.

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

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

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. 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 reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data 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.

For purposes of this Annual Report on Form 10-K, including the footnotes to our consolidated financial statements, (i) with respect to our collaboration for pralsetinib, Roche means F. Hoffmann-La Roche Ltd and Genentech, Inc., and (ii) with respect to our cancer immunotherapy collaboration, Roche means F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc.

PART I

Item 1. Business.

Overview

We are a global precision therapy company that is inventing life-changing medicines for people with cancer and blood disorders. Applying an approach that is both precise and agile, we create therapies that selectively target genetic drivers, with the goal of staying one step ahead across stages of disease. Since 2011, we have leveraged our research platform, including expertise in molecular targeting and world-class drug design capabilities, to rapidly and reproducibly translate science into a broad pipeline of precision therapies. Today, we are delivering our approved medicines, AYVAKIT®/AYVAKYT® (avapritinib) and GAVRETO® (pralsetinib), to patients in the U.S. and Europe, and we are globally advancing multiple programs for systemic mastocytosis, or SM, lung cancer and other genomically defined cancers, and cancer immunotherapy.

Our drug discovery approach combines our biological insights with our proprietary compound library and chemistry expertise to design highly selective and potent precision therapies, with the goal of delivering significant and durable clinical benefit to patients based on the genetic driver of their disease. This uniquely targeted, scalable approach is designed to empower the rapid design and development of new treatments and increase the likelihood of success. In addition, our business model integrates our research engine with robust clinical development and commercial capabilities in oncology and hematology to create a cycle of innovation.

Systemic Mastocytosis and other Mast Cell Disorders — AYVAKIT®/AYVAKYT® (avapritinib) and BLU-263

Avapritinib

We are developing and commercializing avapritinib for the treatment of advanced SM, and developing avapritinib for the treatment of non-advanced SM. SM is a rare hematologic disorder that causes an overproduction of mast cells and the accumulation of mast cells in the bone marrow and other organs, which can lead to a wide range of debilitating symptoms and, in advanced forms of the disease, organ dysfunction and failure. Nearly all cases of SM are driven by the KIT D816V mutation, which aberrantly activates mast cells.

We are evaluating avapritinib in an ongoing registration-enabling Phase 1 clinical trial in advanced SM, which we refer to as our EXPLORER trial, and an ongoing registration-enabling Phase 2 clinical trial in advanced SM, which we refer to as our PATHFINDER trial. In April 2021, we presented registration-enabling data from the PATHFINDER trial at the virtual American Association for Cancer Research, or AACR, Annual Meeting.

In June 2021, the FDA approved avapritinib under the brand name AYVAKIT for the treatment of adult patients with advanced SM, including aggressive SM or ASM, SM with an associated hematologic neoplasm or SM-AHN, and mast cell leukemia or MCL. In January 2022, the Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, adopted a positive opinion recommending marketing authorization for avapritinib as a monotherapy for the treatment of adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy. Pending the European Commission's final decision on our Type 2 variation marketing authorisation application, or MAA, we anticipate obtaining regulatory approval from the EMA and launching avapritinib under the brand name AYVAKYT for advanced SM in Europe in the second quarter of 2022.

In addition, through our distribution agreement with Neopharm Israel Ltd., a marketing authorization application in Israel was submitted in June 2021 for avapritinib for patients with advanced SM and PDGFRA exon 18 mutant gastrointestinal stromal tumors, or GIST. In the future, we plan to pursue the regulatory approval and commercialization of avapritinib in additional global geographies, including through additional potential distribution agreements.

In addition, we are evaluating avapritinib in an ongoing registration-enabling Phase 2 clinical trial in non-advanced SM, which we refer to as our PIONEER trial. In January 2022, we announced that the PIONEER trial was

fully enrolled. We plan to report top-line data for Part 2 of the PIONEER trial in mid-2022 and to submit a supplemental new drug application, or sNDA, to the FDA for avapritinib in non-advanced SM in the second half of 2022.

The FDA has granted breakthrough therapy designation to avapritinib for (i) the treatment of advanced SM, including the subtypes of ASM, SM-AHN and MCL, and (ii) the treatment of moderate to severe indolent SM. In addition, the FDA has granted orphan drug designation to avapritinib for the treatment of mastocytosis, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of mastocytosis.

BLU-263

We are developing BLU-263, an investigational, orally available, potent and highly selective KIT inhibitor, for the treatment of non-advanced SM and other mast cell disorders. BLU-263 is designed to have equivalent potency as avapritinib, with low off-target activity and lower penetration of the central nervous system, or CNS, relative to avapritinib based on preclinical data, which we believe will enable development of BLU-263 in a broad population of patients with non-advanced SM, including patients with lower disease burden and potentially patients with other mast cell disorders.

In April 2021, we presented results from a Phase 1 trial of BLU-263 in healthy volunteers at the virtual AACR Annual Meeting, which showed that BLU-263 was well-tolerated at all doses tested. Based on these data, we initiated a Phase 2/3 trial of BLU-263 in patients with non-advanced SM, which we refer to as our HARBOR trial, in the second quarter of 2021. We anticipate presenting initial data from the HARBOR trial in the second half of 2022.

RET-Altered Cancers — GAVRETO® (pralsetinib)

We are developing and commercializing pralsetinib for the treatment of RET fusion-positive non-small cell lung cancer, or NSCLC, and for the treatment of RET-altered thyroid carcinoma, including medullary thyroid carcinoma, or MTC. We are also developing pralsetinib for the treatment of other RET-altered solid tumors. We have granted exclusive licenses to Roche and CStone Pharmaceuticals, or CStone, to develop and commercialize pralsetinib in their respective territories. See "*—Collaborations and Licenses Summary*" below.

Pralsetinib received accelerated approval in the U.S. under the brand name GAVRETO for the treatment of (i) adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test, (ii) adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC who require systemic therapy, and (iii) adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

In November 2021, Roche announced that the European Commission granted conditional marketing authorization for GAVRETO as a monotherapy for the treatment of adults with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor. Roche submitted a Type II variation MAA to the EMA for pralsetinib for RET-altered thyroid cancers in December 2021, as well as marketing applications for pralsetinib for RET-altered NSCLC and thyroid cancers across multiple global geographies in 2021. Marketing applications are planned for pralsetinib for RET-altered NSCLC and thyroid cancers across additional global geographies in 2022.

In March 2021, China's National Medical Products Administration, or NMPA, approved GAVRETO for the treatment of RET fusion-positive NSCLC patients previously treated with platinum-based chemotherapy. In April 2021, China's NMPA accepted CStone's new drug application, or NDA, with Priority Review designation, for pralsetinib for the treatment of RET-mutant MTC and RET fusion-positive thyroid cancer.

We are currently evaluating pralsetinib in an ongoing registration-enabling Phase 1/2 clinical trial in patients with RET-altered NSCLC, MTC and other advanced solid tumors, which we refer to as the ARROW trial. In addition, Roche is conducting multiple ongoing studies, including a registration-enabling Phase 3 clinical trial in treatment-naïve patients with RET fusion-positive NSCLC, which is referred to as the ACCELERET-Lung trial; and, a registration-enabling Phase 3 clinical trial in patients with locally advanced or metastatic RET-mutated MTC who have not previously received a standard of care multi-kinase inhibitor therapy, which is referred to as the ACCELERET-MTC

trial. In June 2021, we reported updated data from the ARROW trial in metastatic RET fusion-positive NSCLC and other advanced solid tumors at the 2021 American Society of Clinical Oncology, or ASCO, Annual Meeting. The ARROW trial was fully enrolled in December 2021. Pursuant to our collaboration with Roche, we are co-developing pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, as well as other solid tumors.

The FDA has granted breakthrough therapy designation to pralsetinib for (i) the treatment of patients with RET fusion-positive NSCLC that has progressed following platinum-based chemotherapy, and (ii) the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments. In addition, the FDA has granted orphan drug designation to pralsetinib for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC.

PDGFRA-Driven Gastrointestinal Stromal Tumors — AYVAKIT® / AYVAKYT® (avapritinib)

We are commercializing avapritinib for the treatment of patients with PDGFRA exon 18 mutant GIST, a rare disease that is a sarcoma, or tumor of bone or connective tissue, of the gastrointestinal tract. The FDA has granted breakthrough therapy designation for avapritinib for the treatment of unresectable or metastatic GIST harboring the PDGFRA D842V mutation. In addition, the FDA has granted orphan drug designation to avapritinib for the treatment of GIST, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of GIST. Avapritinib is approved in the U.S. under the brand name AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations, and is approved in Europe with conditional marketing authorization under the brand name AYVAKYT as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring a PDGFRA D842V mutation.

In March 2021, CStone announced that China's NMPA approved AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. AYVAKIT received accelerated approval in April 2021 from the Taiwan Food and Drug Administration, or TFDA, and approval in Hong Kong in December 2021, both for adults with unresectable or metastatic GIST harboring PDGFRA D842V mutations.

EGFR-Mutated NSCLC – BLU-701, BLU-945 and BLU-451

We are developing three investigational EGFR inhibitors, BLU-701, BLU-945 and BLU-451, which was formerly known as LNG-451, with the goal of addressing the nearly all activating mutations (>90 percent) in EGFR-driven NSCLC. The introduction of EGFR-targeted therapies, including osimertinib, has transformed the care of patients with EGFR-driven NSCLC; however, there is a significant need for new treatment options designed to prevent a broad range of resistance mechanisms before they emerge, with the goal of prolonging patient benefit. In addition, there are no approved targeted therapies for patients with disease progression following osimertinib, and limited treatment options for patients with EGFR exon 20 insertion-positive NSCLC.

BLU-701 and BLU-945 were specifically designed to provide comprehensive coverage of common activating and on-target resistance mutations, spare wild-type EGFR and other kinases to limit off-target toxicities, and treat or prevent CNS metastases, which occur frequently in patients with EGFR-driven NSCLC. We believe these profiles may enable BLU-701 and BLU-945 to become the backbones of a range of combination strategies with the potential to address important medical needs for patients with EGFR-driven NSCLC, including in early line treatment settings. We plan to develop BLU-701 and BLU-945 in combination with each other and other therapies, including osimertinib, as an initial treatment designed to prevent resistance from emerging. In addition, we plan to develop BLU-701 and BLU-945 as monotherapies in certain biomarker-selected patient populations.

In December 2021, we completed our acquisition of Lengo Therapeutics, Inc., along with its lead compound LNG-451, which we now refer to as BLU-451. BLU-451 is an oral precision therapy in development for the treatment of NSCLC in patients with EGFR exon 20 mutations.

EGFR-Positive NSCLC — BLU-701

BLU-701 is a selective and potent investigational inhibitor of EGFR harboring either the activating L858R or exon 19 deletion mutations combined with the acquired C797S mutation, the most common on-target resistance mutation to osimertinib. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, BLU-701 showed strong and durable inhibition of tumor growth at doses that are EGFR wild-type sparing, and the potential to be used in both first- and second-line settings. BLU-701 indicated significant CNS penetration in preclinical models, with comparable exposure in the plasma and brain, which illustrates its potential to treat or prevent CNS metastases in patients with EGFR-driven tumors. Based on these preclinical data, we initiated a Phase 1/2 trial of BLU-701 in EGFR-mutant NSCLC, which we refer to as our HARMONY trial, in the fourth quarter of 2021. We plan to present initial clinical data from the HARMONY trial in the second half of 2022.

EGFR-Positive NSCLC — BLU-945

BLU-945 is a selective and potent investigational inhibitor of EGFR harboring either the activating L858R or exon 19 deletion mutations combined with the acquired T790M and C797S mutations, the most common on-target resistance mutations to first-generation EGFR inhibitors and osimertinib, respectively. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, BLU-945 demonstrated potent antitumor activity in osimertinib-resistant tumor models, as well as activity in an intracranial patient-derived xenograft model. Both preclinical models harbored activating mutations combined with the T790M and C797S mutations. Based on these preclinical data, we initiated a Phase 1/2 trial of BLU-945 in patients with EGFR-driven NSCLC, which we refer to as our SYMPHONY trial, in the second quarter of 2021. We plan to present initial clinical data from the SYMPHONY trial in the second quarter of 2022.

EGFR-Positive NSCLC – Combinations with BLU-701 and/or BLU-945

Based on their differentiated selectivity profiles and potency against on-target EGFR activating and resistant mutants, we believe BLU-701 and BLU-945 have the potential to become backbone therapies for a range of combination strategies for EGFR-positive NSCLC across multiple treatment lines, potentially including combinations of BLU-701 or BLU-945 with other EGFR therapies or treatment modalities, as well as BLU-701 and BLU-945 together. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, the combination of BLU-945 with either gefitinib or osimertinib showed enhanced antitumor activity when compared with either gefitinib or osimertinib alone. At the British Thoracic Oncology Group, or BTOG, Annual Conference in January 2022, we reported preclinical data supporting the development of BLU-701 and BLU-945 combination therapy in EGFR-driven NSCLC. Based on these results, we plan to develop BLU-701 and BLU-945 in combination with each other and other agents.

EGFR Exon 20 Insertion-Positive NSCLC — BLU-451

BLU-451 is a selective and potent investigational inhibitor under development for the treatment of EGFR exon 20 insertion-positive NSCLC. Based on preclinical data, BLU-451 potently inhibited all common EGFR exon 20 insertion variants with marked selectivity over wild-type EGFR and off-target kinases, and has shown significant CNS penetration. We recently received clearance for an investigational new drug, or IND, application for BLU-451 for EGFR exon 20 insertion-positive NSCLC. In the first quarter of 2022, we plan to initiate a Phase 1/2 trial of BLU-451 in EGFR exon 20 insertion-positive NSCLC, and we expect to present preclinical data for BLU-451 in the second quarter of 2022.

Cyclin E Aberrant Cancers – BLU-222

We are developing an investigational inhibitor, BLU-222, targeting CDK2 for the treatment of patients with cyclin E aberrant cancers. In subsets of patients across multiple cancer types, aberrant cyclin E, or CCNE1, hyperactivates CDK2, resulting in cell cycle dysregulation and tumor proliferation. Aberrant CCNE1 has been observed as a primary driver of disease, as well as a mechanism of resistance to CDK4/6 inhibitors and other therapies.

At the virtual AACR Annual Meeting in April 2021, we presented preclinical data showing that selective CDK2 inhibition arrested the cell cycle and blocked tumor proliferation in CCNE1-amplified cell lines, and demonstrated robust and sustained antitumor activity in vivo in models of CCNE1-amplified ovarian, breast and gastric cancer. A selective CDK2 inhibitor also showed improved tolerability compared to a pan-CDK inhibitor and chemotherapy, as measured by animal body weight.

We recently received FDA clearance for an IND application for BLU-222 for cyclin E aberrant cancers. We plan to initiate a Phase 1/2 trial of BLU-222 in cyclin E aberrant cancers, which we refer to as our VELA trial, in the first quarter of 2022, and to present preclinical data for BLU-222 in the second quarter of 2022. BLU-222 is being developed as a single agent and in combination with chemotherapy in gynecological cancers, and in combination with hormonal and the approved CDK-4/6 inhibitor ribociclib for hormone-receptor-positive, HER2-negative breast cancer.

Advanced Cancers – BLU-852

BLU-852 is a selective and potent investigational inhibitor of MAP4K1, a well-characterized immunokinase involved in the regulation of immune cells. Preclinical data presented at the virtual AACR Annual Meeting in April 2021 show that MAP4K1 inhibition enhanced intratumoral immune cell activation, overcame regulatory T cell, or Treg, mediated T cell suppression, and reduced tumor burden both as a monotherapy and in combination with checkpoint inhibition. These preclinical data support the continued development of BLU-852. Under our ongoing cancer immunotherapy collaboration, we expect Roche to initiate a Phase 1 trial of BLU-852, as a single agent and in combination with atezolizumab, in advanced cancers in 2023.

Fisogatinib — Hepatocellular Carcinoma

Fisogatinib is an investigational, orally available, potent and highly selective inhibitor that targets FGFR4, a kinase that is aberrantly activated in a defined subset of patients with hepatocellular carcinoma, or HCC. Following a strategic evaluation of the evolving HCC treatment landscape and prioritization of resources across our broad precision therapy pipeline, we have decided to deprioritize our clinical development of fisogatinib for the treatment of advanced HCC. We have discontinued further enrollment of the Blueprint Medicines-sponsored clinical trial of fisogatinib as a monotherapy and in combination with sugemalimab, an anti-PD-L1 immunotherapy being developed by CStone. CStone continues to retain development and commercial rights to fisogatinib in the CStone territory, which encompasses Mainland China, Hong Kong, Macau and Taiwan.

Discovery Platform

We plan to continue to leverage our discovery platform to systematically and reproducibly identify kinases that are drivers of diseases in genomically defined patient populations, and craft drug candidates that potently and selectively target these kinases. In addition, we plan to expand our discovery platform by building capabilities, supported by external collaborations, for targeted protein degradation of both kinase and non-kinase targets in precision oncology, with the goal of advancing transformative therapies to patients and further broadening the significant productivity of our research engine. Beyond the discovery programs described above, we have multiple pre-development candidate programs for undisclosed kinase targets. In 2022, we plan to nominate two development candidates from our discovery programs. We also plan to share our vision for our expanded discovery platform at an R&D Day in the second half of 2022.

Under our immunotherapy collaboration with Roche, we are conducting activities for up to two discovery programs, including BLU-852. See "*—Collaborations and Licenses Summary*" below.

Collaborations and Licenses Summary

Roche—Immunotherapy Collaboration. In March 2016, we entered into a collaboration with Roche to discover, develop and commercialize small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy (including the kinase target MAP4K1, which is believed to play a role in T cell regulation), as single products or possibly in combination with other therapeutics.

Roche—Pralsetinib Collaboration. In July 2020, we entered into a collaboration with Roche to develop and commercialize pralsetinib for the treatment of RET-altered cancers. Under the collaboration, we and Genentech are co-commercializing GAVRETO in the U.S., and Roche has exclusive commercialization rights for pralsetinib outside of the U.S., excluding the CStone territory. We and Roche are also co-developing pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, and expanding development of pralsetinib in multiple treatment settings.

CStone. In June 2018, we entered into a collaboration with CStone to develop and commercialize avapritinib, pralsetinib and fisogatinib, as well as back-up forms and certain other forms, in the CStone territory either as a monotherapy or as part of a combination therapy.

Clementia. In October 2019, we entered into a license agreement with Clementia Pharmaceuticals, Inc., or Clementia, a wholly-owned subsidiary of Ipsen S.A., and granted Clementia an exclusive, worldwide, royalty-bearing license to develop and commercialize BLU-782, as well as specified other compounds related to the BLU-782 program. BLU-782 is an investigational, orally available, potent and highly selective inhibitor that targets mutant activin-like kinase 2, or ALK2, in development for the treatment of fibrodysplasia ossificans progressiva, or FOP. The FDA has granted a rare pediatric disease designation, orphan drug designation and fast track designation to BLU-782, each for the treatment of FOP. Clementia initiated patient dosing in a Phase 2 clinical trial of BLU-782, now referred to as IPN60130, in the first quarter of 2022.

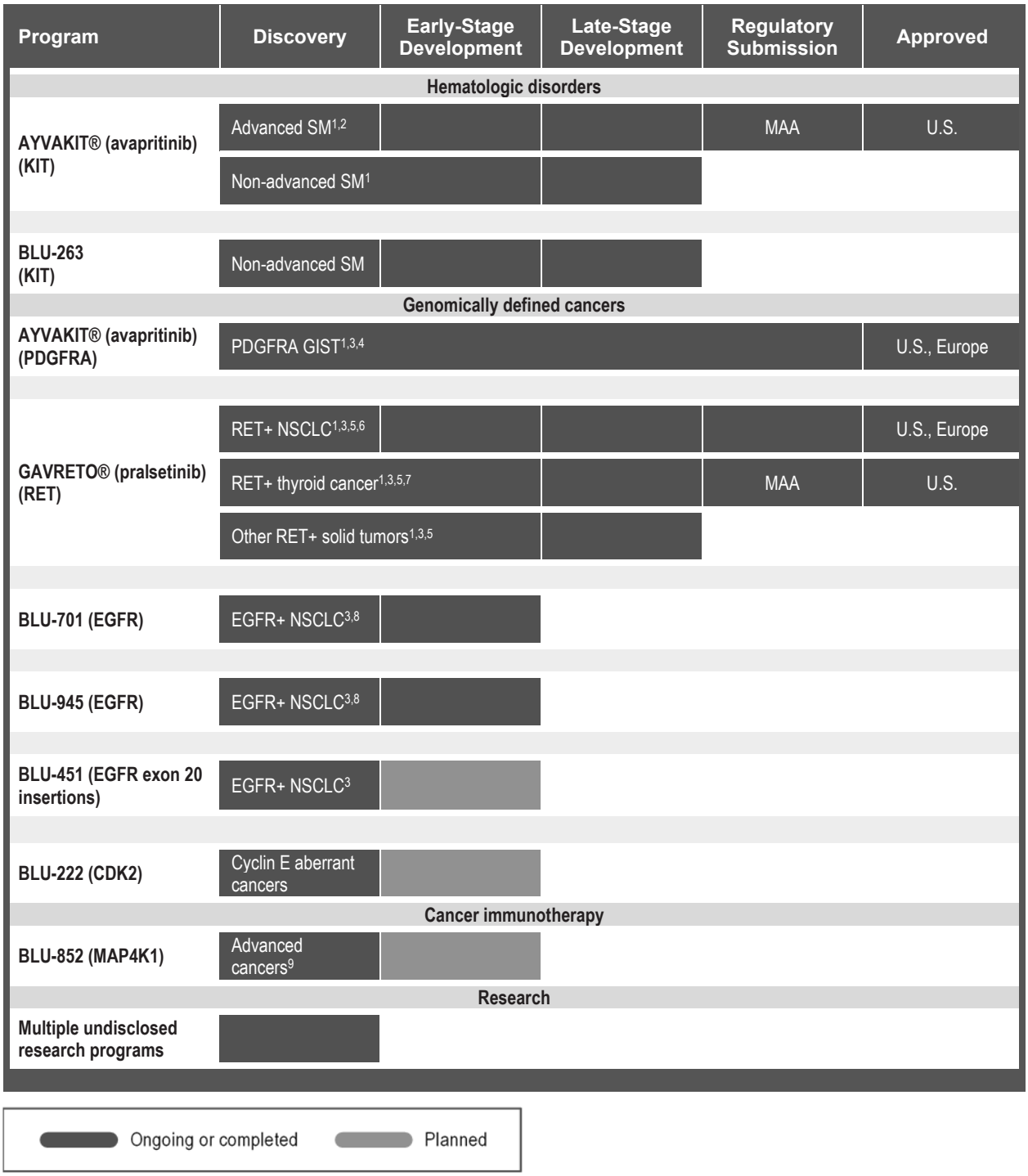
Zai Lab. In November 2021, we entered into a collaboration with Zai Lab to develop and commercialize BLU-701 and BLU-945 for the treatment of EGFR-driven NSCLC in Greater China, including Mainland China, Hong Kong, Macau and Taiwan. The collaboration aims to accelerate and expand global development of BLU-701 and BLU-945.

Mergers & Acquisitions Summary

Lengo Therapeutics. In December 2021, we completed our acquisition of Lengo Therapeutics, Inc., along with its lead compound LNG-451, now known as BLU-451, which is in development for the treatment of NSCLC in patients with EGFR exon 20 insertion mutations. The acquisition also included additional undisclosed preclinical precision oncology programs and research tools, including a catalog of covalent, highly brain penetrant kinase inhibitors that we plan to add to our proprietary compound library to further enable future drug discovery efforts.

We will continue to evaluate additional collaborations, acquisitions, partnerships and licenses that could maximize the value of our programs and allow us to leverage the expertise of strategic collaborators, partners and licensors, including in additional geographies where we may not have current operations or expertise. We are also focused on engaging in collaborations, acquisitions, partnerships and license agreements to capitalize on or expand our discovery platform.

Our Pipeline



(1) CStone has exclusive rights to develop and commercialize avapritinib, pralsetinib and fisogatinib in Mainland China, Hong Kong, Macau and Taiwan. For more information, see "—Collaborations and Licenses" below.
(2) Approved in the U.S. for the treatment of adults with advanced SM, including ASM, SM-AHN and MCL. Received a positive opinion from the EMA's CHMP for the treatment of adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy.
(3) Unresectable or metastatic disease.
(4) Approved in the U.S. for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations.
(5) Received conditional marketing authorization in Europe under the brand name AYVAKYT for the treatment of adults with unresectable or metastatic GIST harboring the PDGFRA D842V mutation.
(6) In collaboration with Roche. Blueprint Medicines and Roche have co-exclusive rights to develop and commercialize pralsetinib in the U.S., and Roche has exclusive rights to develop and commercialize pralsetinib outside the U.S., excluding the CStone territory. For more information, see "—Collaborations and Licenses" below.
(7) Received accelerated approval in the U.S. for the treatment of adults with metastatic RET fusion-positive NSCLC. Continued approval may be contingent on a confirmatory trial. Received conditional marketing authorization in Europe for the treatment of adults with advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor.
(8) Received accelerated approval in the U.S. for the treatment of patients with advanced or metastatic RET-mutant MTC and RET fusion-positive thyroid cancer. Continued approval may be contingent on confirmatory trials.
(9) Zai Lab has exclusive rights to develop and commercialize BLU-701 and BLU-945 in Mainland China, Hong Kong, Macau and Taiwan. For more information, see "—Collaborations and Licenses" below.
(10) In collaboration with Roche. Blueprint Medicines and Roche are conducting activities for up to two programs under the collaboration, including the program targeting MAP4K1. For one of the programs, Blueprint Medicines has U.S. commercial rights and Roche has ex-U.S. commercialization rights. For one of the programs, Roche has worldwide commercialization rights. For more information, see "—Collaborations and Licenses" below.

Our Strategy

As a fully-integrated, global precision therapy company focused on discovering, developing and commercializing a portfolio of precision therapies, our vision is to bring life-changing precision therapies to as many patients with cancer and blood disorders as possible. To achieve this goal, key elements of our strategy are as follows:

- Accelerate the adoption of our approved medicines, AYVAKIT and GAVRETO in the U.S. and AYVAKYT in Europe, continue to strengthen and expand our global commercial capabilities and prepare for additional planned commercial launches in additional indications, including non-advanced SM.

- Deepen our strategic focus on SM and related mast cell disorders by seeking regulatory approval for avapritinib for the treatment of non-advanced SM and developing BLU-263 for the treatment of non-advanced SM, as well as exploring opportunities to address the needs of additional patient populations with adjacent hematologic disorders.

- Advance the global development and commercialization of pralsetinib and seek international regulatory approvals under the Roche pralsetinib collaboration as a treatment for RET-altered cancers.

- Advance our innovative research programs, including BLU-701, BLU-945 and BLU-451, our selective and potent EGFR inhibitors for EGFR-driven NSCLC, BLU-222, our selective and potent CDK2 inhibitor for cyclin E aberrant cancers, and our other preclinical programs, rapidly through development with plans to seek regulatory approval.

- Expand our broad, differentiated precision medicine pipeline, with a focus on genomically defined cancers and blood disorders and continued internal discovery research and innovation, as well as opportunities to acquire or in-license complementary technologies or therapies.

- Evaluate potential additional collaborations, partnerships and licenses that could maximize the value of our existing programs and allow us to leverage the expertise of strategic collaborators, partners and licensors, including in additional geographies where we may not have current operations or expertise.

- Maintain a commitment to building a corporate culture centered by our focus on patient needs, science-driven approach to drug development, and organizational strength through the diversity of experience and perspective across our workforce.

Our Precision Therapy Approach

Our approach is to systematically and reproducibly identify drivers of disease in genomically defined patient populations and to craft drug candidates that provide significant and durable clinical responses to patients. This approach enables us to drug known targets that have been difficult to inhibit selectively and also identify, characterize and design drug candidates to inhibit novel targets. By focusing on diseases in genomically defined patient populations, we believe that we can quickly identify the patients most likely to respond, resulting in a more efficient development path with a greater likelihood of success. To date, our approach has been enabled by our drug discovery platform consisting of two pillars: (1) a proprietary, highly-annotated library of novel compounds; and (2) a novel target discovery engine, which is a comprehensive process that interrogates kinase biology from many angles using genomics, structural biology and cell biology.

We have initially focused our efforts on kinase drug discovery and development. Kinases are enzymes that function in many signaling pathways to regulate critical cellular functions. Kinase-dependent signaling networks are present in multiple different cell types and deregulation of these networks can lead to disease pathology. Abnormal activation of kinases has been shown to drive several key activities of cancer cells, including growth, survival, metabolism, cell motility and angiogenesis. Kinases may become abnormally activated through a number of mechanisms, including when: (1) a gene mutates creating a change in the resulting protein sequence; (2) chromosomes become rearranged creating a translocation or a fusion gene; or (3) excessive amounts of protein are created due to gene duplication or dysregulation leading to overexpression. There is a strong link between genomic alterations in kinases and disease, including specific forms of cancer and rare diseases. Several kinases have been validated as oncogenes, which are genes that when altered can initiate and maintain cancer growth. Ongoing genomic analyses of tumor data sets continue to identify new roles for kinases as drivers of disease.

We believe there is substantial opportunity for developing novel and transformative therapies that target well characterized but currently difficult-to-drug kinases as well as kinases of unknown biology which constitute the majority of the kinome, by:

- ***Crafting very selective kinase drugs.*** Due to the high degree of homology between kinases, specific targeting of a given kinase can be challenging. Many of the approved kinase drugs inhibit multiple kinases and are referred to as multi-kinase inhibitors. Due to inhibition of off-target kinases, these multi-kinase inhibitors often give rise to severe unwanted effects, which can negatively impact the ability to dose patients at sufficient levels to achieve optimal efficacy. We believe increasing selectivity will minimize off-target toxicities and will improve efficacy by enabling higher dose levels and greater target inhibition. Further, combination therapies require that the drugs have non-overlapping toxicities, which could be minimized with more selective agents.

- ***Generating novel chemical matter required to target difficult-to-drug kinases.*** Novel chemical matter is needed to address targets that are known but have proven difficult-to-drug. Pharmaceutical companies generally rely on known chemical families as the basis of drug discovery programs. Consequently, the vast majority of pharmaceutical companies have similar compound libraries. New approaches are needed to develop novel chemistry and differentiated libraries that can inhibit difficult-to-drug kinases in alternate ways.

- ***Overcoming resistance mediated by the alteration of kinase targets, and helping solve for intractable sites of progression, such as the brain.*** Most approved kinase inhibitors provide only temporary disease control. Patients may relapse due to the emergence of on-target resistance mutations or in cancer, tumors progress because therapies are unable to cross the blood-brain barrier to treat or prevent CNS metastases. Novel approaches, including innovative combinations, are needed to predict and inhibit resistant mutants and address common sites of progression including the brain, thus providing more durable clinical responses.

In addition, we plan to expand our discovery platform by building capabilities, supported by external collaborations, for targeted protein degradation of both kinase and non-kinase targets in precision oncology, with the goal of advancing transformative therapies to patients and further broadening the significant productivity of our research engine.

Disease Overviews

Systemic Mastocytosis (SM)

SM is a disorder of the mast cells, the key effector cells of allergic inflammation, which have several physiologic roles including wound healing, regulation of vascular and epithelial permeability and immune cell recruitment. The signature of SM is the overproduction of mast cells and the accumulation of mast cells in the bone marrow and other organs. In advanced forms of SM, abnormal mast cells may also accumulate in the liver, spleen, gastrointestinal tract and bones. Mast cell activation and histamine release can lead to severe allergic symptoms ranging from a skin rash to hives, fever and anaphylaxis, while mast cell accumulation in advanced cases of SM can eventually lead to organ dysfunction and failure.

SM comprises a spectrum of disease, with nearly all patients (approximately 95 percent) having a KIT D816V mutation, the underlying driver of disease for most SM patients. The diagnosis, which is usually made in adulthood, involves a complex diagnostic algorithm that begins with confirmation of SM and subsequently categorizes patients into non-advanced or advanced subtypes of disease. Indolent SM, a subset of non-advanced SM, is the most common form of SM and is characterized by often severe, unpredictable and debilitating symptoms due to mast cell activation. Symptoms may include hypersensitivity reactions, including unpredictable anaphylaxis, gastrointestinal distress including severe nausea, vomiting and diarrhea, and extensive skin rashes that cause pain, discomfort and social isolation. Advanced SM is a more rare form of SM associated with mast cell infiltration of organ systems resulting in increasingly severe impact on life expectancy, and includes three subsets: ASM, SM-AHN, and MCL. These advanced forms of SM have historically had a median overall survival of less than six months to 3.5 years and are characterized by prominent organopathy and dysfunction, as well as the debilitating symptoms of mast cell activation.

Advanced SM accounts for approximately 5-10 percent of the patients, or about 5,000 patients in the U.S., France, Germany, Italy, Spain, the United Kingdom and Japan, which we collectively refer to as the Major Markets. Non-advanced SM, including indolent SM and an intermediate form referred to as smoldering SM, account for the remaining 90-95 percent of patients, or about 70,000 patients in Major Markets. Population studies estimate the prevalence rate of all subtypes of SM is approximately 9.6 per 100,000 people.

The current treatment paradigm for SM varies by disease subtype. Currently, there are no approved targeted therapies other than avapritinib designed to potently and selectively inhibit the KIT D816V mutation. There are two approved therapies for advanced SM: midostaurin and imatinib. Midostaurin is a multi-kinase inhibitor with limited KIT D816V inhibitory activity. Imatinib is approved only for patients with the ASM subtype who do not harbor the KIT D816V mutation, or who have an unknown mutation status. Other treatments used in advanced SM include interferon alpha or cytoreductive agents to reduce mast cell burden, or treatments aimed at addressing the associated blood disorder.

For patients with non-advanced SM, management is symptom-directed and includes avoidance of triggers of mast cell activation (such as insect stings). Treatments for non-advanced SM include histamine blockers, cromolyn, epinephrine, corticosteroids, and, in cases of refractory patients, cytoreductive agents. Patients often take multiple symptom-directed treatments to manage their disease, and a reduction in polypharmacy burden is an important treatment goal. Within non-advanced SM, key opinion leaders see the greatest degree of medical need for a significant portion of patients who have a heavy symptom burden that current therapies fail to address.

We are developing avapritinib for the treatment of SM and BLU-263 for the treatment of non-advanced SM and other mast cell disorders. Previously reported clinical data of avapritinib for patients with SM are described below. In April 2021, we presented results from a Phase 1 trial of BLU-263 in healthy volunteers at the virtual AACR Annual Meeting, which showed that BLU-263 was well-tolerated at all doses tested. In January 2021, we announced positive topline results of BLU-263 in a Phase 1 healthy volunteer trial. Based on these data, we initiated the Phase 2/3 HARBOR trial of BLU-263 in patients with non-advanced SM in the second quarter of 2021.

Clinical Trial Data in SM

Avapritinib—Phase 1 EXPLORER Trial and Phase 2 PATHFINDER Trial

We are evaluating avapritinib for the treatment of patients with advanced SM in our registration-enabling EXPLORER and PATHFINDER clinical trials. The EXPLORER trial is an open-label, single-arm Phase 1 trial. The PATHFINDER trial is an open-label, single-arm Phase 2 trial. Both trials have completed enrollment. For both the EXPLORER and PATHFINDER trials, key endpoints include overall response rate, or ORR, duration of response, or DOR, quantitative measures of mast cell burden, patient-reported outcomes and safety.

Data Presented at the Virtual American Association for Cancer Research Annual Meeting in April 2021

In a pre-specified interim analysis from the PATHFINDER trial, 32 patients who primarily received a starting avapritinib dose of 200 mg once daily were evaluable for response per the modified IWG-MRT-ECNM criteria, as of a data cutoff date of June 23, 2020. ORR was defined as complete remission with full or partial recovery of peripheral blood counts, or CR/CRh, partial remission or clinical improvement. The confidence interval, or CI, represents the confidence interval of the reported endpoints. Response assessments were completed per central review, and all reported clinical responses were confirmed.

Clinical Activity Data. Overall, the ORR was 75 percent (95% CI: 57%, 89%), and the CRh rate was 19 percent, with a median time to CRh of 5.6 months. These results show that responses deepened over time at a rate consistent with previously reported EXPLORER trial results. Avapritinib led to robust and durable benefits across a number of additional clinical activity measures. In new patient-reported outcomes data, avapritinib showed a statistically significant reduction in total symptom score after 40 weeks ($p<0.001$), as measured by the Advanced SM Symptom Assessment Form. Treatment with avapritinib resulted in robust improvements in patient-reported quality of life, based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Across multiple measures of mast cell burden, avapritinib showed profound reductions in serum tryptase, bone marrow mast cells, KIT D816V allele burden and spleen volume.

Safety Data. Avapritinib was generally well-tolerated in 62 patients enrolled in the PATHFINDER trial, and most adverse effects, or AEs, were reported as Grade 1 or 2. The most common treatment-emergent AEs reported by investigators greater than or equal to 15 percent were peripheral edema, periorbital edema, thrombocytopenia, anemia, neutropenia, diarrhea, nausea, vomiting and fatigue. Three patients, or 5 percent, discontinued avapritinib due to treatment-related AEs, and most patients, or 84 percent, have remained on treatment as of the data cutoff date.

Data Published in Nature Medicine in December 2021

Across the EXPLORER and PATHFINDER trials, 148 patients with advanced SM were enrolled as of a data cutoff date of May 27, 2020 for the EXPLORER trial and June 23, 2020 for the PATHFINDER trial. ORR was defined as CR/CRh, partial remission or clinical improvement. Response assessments were completed per central review, and all reported clinical responses were confirmed.

Clinical Activity Data. In the EXPLORER trial, 53 patients were response evaluable, and the ORR was 75 percent (95% CI: 62%, 86%). The median DOR was 38 months (95% CI: 22 months, not estimable). The estimated 24-month overall survival rate was 76 percent. Responses reported in the PATHFINDER pre-specified interim analysis of 32 evaluable patients were consistent with previously reported data. Across both studies, statistically significant improvements in patient-reported symptoms were observed, as measured by the Advanced SM Symptom Assessment Form Total Symptom Score. Avapritinib showed broad activity across all advanced SM subtypes, including SM-AHN. In the PATHFINDER trial, substantial reductions were observed in monocytosis in patients with SM and chronic myelomonocytic leukemia, and in eosinophilia in patients with SM and chronic eosinophilic leukemia, potentially reflecting the multi-lineage involvement of the KIT D816V mutation.

Safety Data. Avapritinib was generally well-tolerated, consistent with previously reported results. The most common treatment-emergent AEs included edema, thrombocytopenia, anemia, diarrhea, nausea, fatigue, vomiting,

neutropenia, headache, cognitive effects and abdominal pain. Overall, 10 percent of patients in the EXPLORER trial and 5 percent of patients in the PATHFINDER trial discontinued avapritinib due to treatment-related AEs.

Avapritinib—Phase 2 PIONEER Trial

PIONEER is a randomized, double-blind, placebo-controlled, registration-enabling trial evaluating avapritinib in patients with non-advanced SM. The trial includes three parts: dose-finding Part 1, registration-enabling Part 2 and long-term treatment Part 3. All patients who complete Parts 1 or 2 will have an opportunity to receive treatment with avapritinib in Part 3. Key trial endpoints include the change in patient-reported disease symptoms as measured by the Indolent SM Symptom Assessment Form Total Symptom Score, or ISM-SAF TSS, quantitative measures of mast cell burden and safety. In January 2022, we announced that the PIONEER trial was fully enrolled.

Previously reported data from Part 1 of the PIONEER trial show that treatment with avapritinib was well-tolerated and resulted in robust and clinically meaningful improvements on measures of mast cell burden, disease symptoms and patient-reported quality of life through 24 weeks. We plan to report top-line data from the registration-enabling Part 2 of the PIONEER trial in mid-2022.

RET-Altered Cancers

RET is a receptor tyrosine kinase that activates multiple downstream pathways involved in cell proliferation and survival. RET can be activated by mutation or when a portion of the RET gene that encodes the kinase domain is joined to part of another gene creating a fusion gene that encodes an aberrantly activated RET fusion protein. RET activating mutations are implicated in advanced MTC (approximately 90 percent of patients), and RET fusions are implicated in several cancers, including papillary thyroid carcinoma (approximately 10- 20 percent of patients) and NSCLC (1-2 percent of patients). We estimate that in the Major Markets, there are approximately 8,900 first-and second-line patients with RET-altered NSCLC and 1,300 patients with MTC, regardless of line of therapy or alteration. In addition, oncogenic RET alterations are observed at low frequencies in colorectal, breast, pancreatic and other cancers, providing a therapeutic rationale for the use of RET inhibitors in multiple patient subpopulations.

The identification of RET fusions as drivers in some cancers prompted the use of approved multi-kinase inhibitors with RET inhibitory activity to treat patients whose tumors express a RET fusion protein. However, we believe these drugs cannot be dosed at levels required to sufficiently inhibit RET due to toxicities that result from inhibition of the primary targets. For example, currently approved therapies such as vandetanib and cabozantinib demonstrate lower objective response rates, or ORR, and DOR in patients with RET-altered NSCLC compared to selective kinase inhibitors targeting other kinase drivers such as EGFR, ALK and ROS1.

One of the greatest challenges in treating cancer is the ability of tumor cells to become resistant to therapy. Kinase reactivation via mutation to evade small molecule inhibition is a common mechanism of resistance. We have predicted future resistance mutations of drugs with RET inhibitory activity. Thus, there is a clear need for a selective RET inhibitor that targets both oncogenic RET fusions and activating mutations and their predicted RET resistance mutations.

Currently, pralsetinib (under the brand name GAVRETO) is the only once-daily RET-targeted therapy approved by the FDA for the treatment of certain RET-altered NSCLC and thyroid cancers in the U.S. Previously reported clinical data of pralsetinib in patients with RET-altered cancers are described below. Pursuant to our collaboration with Roche, we are co-developing pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, as well as other solid tumors.

Clinical Trial Data in RET-Altered NSCLC, Thyroid Cancers, and Other Solid Tumors

Pralsetinib—Phase 1/2 ARROW Trial

The ARROW trial is a Phase 1/2 open-label, registration-enabling trial designed to evaluate the safety, tolerability and efficacy of pralsetinib in adults with RET-altered cancers. The trial consists of two parts: a dose escalation portion and an expansion portion in patients treated at 400 mg once daily. The dose-escalation portion of the

ARROW trial is complete, and as of December 2021, the expansion portion was fully enrolled at multiple sites in the United States, EU and Asia.

Data Presented at the American Society of Clinical Oncology Annual Meeting in June 2021

Efficacy data were reported for patients treated with pralsetinib who were evaluable for response assessment per RECIST 1.1, as determined by blinded independent central review. Response-evaluable populations comprised 216 patients with RET fusion-positive NSCLC who had measurable disease at baseline and received a starting pralsetinib dose of 400 mg once daily, and 19 patients with other RET fusion-positive solid tumors. All results were as of a data cutoff date of November 6, 2020, and all clinical responses were confirmed.

Clinical Activity Data. In 68 treatment-naïve patients with RET fusion-positive NSCLC, the ORR was 79 percent (95% CI: 68%, 88%) and the median DOR was not reached (95% CI: 9.0 months, not reached). For treatment-naïve patients, the initial study protocol limited enrollment to those determined by the investigator to be ineligible for standard platinum-based chemotherapy, which may be due to age, comorbidities or other poor prognostic factors. This eligibility restriction was removed in July 2019, with the goal of including a population more reflective of real-world practice. In an exploratory analysis of treatment-naïve patients enrolled after this expansion of inclusion criteria (n=25), the ORR was 88 percent (95% CI: 69%, 98%). In 126 patients with RET fusion-positive NSCLC who previously received platinum-based chemotherapy, the ORR was 62 percent (95% CI: 53%, 70%) and the median DOR was 22.3 months (95% CI: 15.1 months, not reached).

In a heavily pre-treated population of 19 patients with RET fusion-positive solid tumors beyond NSCLC and thyroid cancer, the ORR was 53 percent (95% CI: 29%, 76%) and the median DOR was 19.0 months (95% CI: 5.5 months, not estimable). Tumor reductions were shown in patients with the following cancers – pancreatic, cholangiocarcinoma, colon, lung except NSCLC, mesenchymal, salivary duct, sweat gland and thymus – as well as patients diagnosed with cancers of unknown primary origin. In the three patients with pancreatic cancer, a particularly difficult-to-treat tumor type, there was one complete response and two partial responses.

Safety Data. A total of 471 patients were enrolled with a pralsetinib dose starting at 400 mg once daily. Across tumor types, pralsetinib was generally well-tolerated with no new safety signals observed. The most common treatment-related AEs reported by investigators greater than or equal to 20 percent were neutropenia, increased aspartate aminotransferase, anemia, decreased white blood cell count, increased alanine aminotransferase, hypertension, constipation and asthenia. Overall, 6 percent of patients discontinued pralsetinib due to treatment-related AEs.

Data Published in The Lancet Oncology and The Lancet Diabetes and Endocrinology in June 2021

The Lancet Oncology published data from the ARROW trial in patients with RET fusion-positive NSCLC, which were consistent with results reported from an updated data cut at the 2021 ASCO Annual Meeting. *The Lancet Diabetes and Endocrinology* simultaneous published results from the ARROW trial in patients with RET-altered thyroid cancer. Efficacy data were reported for patients treated with pralsetinib who were evaluable for response assessment per RECIST 1.1, as determined by blinded independent central review.

Clinical Activity Data. As of a data cutoff date of May 22, 2020, pralsetinib showed robust and durable antitumor activity in patients with RET-altered thyroid cancer who received a starting dose of 400 mg once daily. In 55 patients with RET-mutant MTC previously treated with cabozantinib or vandetanib, the ORR was 60 percent (95% CI: 46%, 73%) and the median DOR was not reached (95% CI: 15.1 months, not estimable). In 21 systemic treatment-naïve patients with RET-mutant MTC, the ORR was 71 percent (95% CI: 48%, 89%) and the median DOR was not reached (95% CI: not estimable, not estimable). In nine patients with RET fusion-positive thyroid cancer, the ORR was 89 percent (95% CI: 52%, 100%) and the median DOR was not reached (95% CI: not estimable, not estimable).

Safety Data. Pralsetinib was generally well-tolerated with safety results consistent with previously reported data. In 142 patients with RET-altered thyroid cancer, the most common treatment-related AEs were increased aspartate aminotransferase, decreased white blood cell count, hypertension, neutropenia, anemia, constipation, asthenia, increased alanine aminotransferase, hyperphosphatemia and lymphopenia. Four percent of patients with RET-altered thyroid cancer discontinued pralsetinib due to treatment-related AEs.

Gastrointestinal Stromal Tumors (GIST)

GIST is a rare disease that is a sarcoma of the gastrointestinal tract. Tumors arise within cells in the wall of the gastrointestinal tract and occur most often in the stomach or small intestine. Most patients are diagnosed between the ages of 50-80 with diagnosis triggered by gastrointestinal bleeding, incidental findings during surgery or imaging, or in rare cases, acute presentation due to tumor rupture or gastrointestinal obstruction. The standard workup at primary presentation includes pathologic confirmation and imaging to assess extent of disease.

The GIST treatment paradigm has advanced dramatically over the past years. Patients diagnosed with localized disease undergo potentially curative tumor resection, while imatinib is given to high risk resected patients to prolong the time to recurrence. The advent of imatinib has improved the prognosis of patients with unresectable or metastatic disease to a five-year median overall survival. Unresectable or metastatic patients typically receive imatinib, followed by sunitinib and regorafenib as the disease progresses.

GIST is a tumor type that depends on continued signaling of a single, aberrantly active kinase. About 5 to 6 percent of primary GIST cases are caused by a PDGFRA D842V mutation, the most common PDGFRA exon 18 mutation. Published data have shown poor outcomes in patients with unresectable or metastatic PDGFRA D842V mutant GIST treated with imatinib and other approved therapies that do not specifically target PDGFRA mutations. Progression can occur within as little as three months, and the median overall survival is 15 months for patients with advanced disease. Currently, AYVAKIT is the only FDA-approved treatment for patients with D842V mutant PDGFRA-driven GIST.

EGFR-Mutated NSCLC

Among the 80 to 85 percent of lung cancers classified as NSCLC, it is estimated that about 10-15 percent of cases in the U.S. and Europe, and about 40-50 percent of cases in Asia are caused by activating EGFR mutations. In recent years, the introduction of EGFR-targeted therapies including osimertinib has dramatically improved outcomes in patients with EGFR-mutated NSCLC. However, there is a significant need for new treatment options designed to prevent a broad range of resistance mechanisms before they emerge, with the goal of prolonging patient benefit. In addition, there are no approved targeted therapies for osimertinib-resistant EGFR-mutated NSCLC, and there are limited treatment options for patients with EGFR exon 20 insertion-positive NSCLC.

We are developing BLU-701 and BLU-945, in combination with each other and other agents, as well as monotherapies in certain biomarker-selected populations, for the treatment of patients with EGFR-mutated NSCLC. We initiated the Phase 1/2 HARMONY trial of BLU-701 in patients with EGFR-driven NSCLC in the fourth quarter of 2021, and initiated the Phase 1 SYMPHONY trial of BLU-945 in patients with EGFR-driven NSCLC in the second quarter of 2021.

We are developing BLU-451 for the treatment of NSCLC in patients with EGFR exon 20 insertion mutations, and we plan to initiate a Phase 1/2 trial for this patient population in the first quarter of 2022.

Cyclin E Aberrant Cancers

Cyclin dependent kinases and their cyclin partners regulate the cell cycle. In certain malignancies, CCNE1 is amplified or overexpressed, hyperactivating CDK2 and leading to cell cycle dysregulation and tumor proliferation. Data from the National Cancer Institute show that CCNE1 amplification is a primary disease driver in subsets of patients with ovarian cancer, endometrial cancer, gastric cancer and a broad range of other solid tumors. For example, approximately 20 percent of patients with ovarian serous cystadenocarcinoma harbor CCNE1 amplifications. In addition, aberrant CCNE1 is a known resistance mechanism in patients with estrogen-receptor-positive breast cancer treated with a CDK4/6 inhibitor. Studies have shown that ovarian and hormone-receptor-positive breast cancer patients with aberrant CCNE1 have poor outcomes. Collectively, these data highlight the broad potential of CDK2 as a therapeutic target.

Prior drug discovery efforts targeting CDK2 have been hindered by challenges in achieving selectivity over other CDK family members associated with toxicity. We are developing BLU-222, a selective and potent investigational

CDK2 inhibitor, for the treatment of patients with cyclin E aberrant cancers. We plan to initiate the Phase 1/2 VELA trial of BLU-222 in cyclin E aberrant cancers in the first quarter of 2022.

Collaborations and Licenses

Roche – Immunotherapy Collaboration

In March 2016, we entered into a collaboration and license agreement, or the Roche immunotherapy agreement, as may be amended from time to time, with Roche for the discovery, development and commercialization of small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy, as single products or possibly in combination with other therapeutics. As a result of an amendment to the Roche immunotherapy agreement in the first quarter of 2021, we and Roche are currently conducting activities for up to two programs under the collaboration, including the previously announced program for the kinase target MAP4K1, which is believed to play a role in T cell regulation.

Under the Roche immunotherapy agreement, as amended, Roche is granted two option rights to obtain an exclusive license to exploit products derived from the collaboration programs in the field of cancer immunotherapy. Such option rights are triggered upon the achievement of Phase 1 proof-of-concept. For one of the collaboration programs, if Roche exercises its option, Roche will receive worldwide, exclusive commercialization rights for the licensed product. For the other collaboration program, if Roche exercises its option, we will retain commercialization rights in the U.S. for the licensed product, and Roche will receive commercialization rights outside of the U.S. for the licensed product. We will also retain worldwide rights to any products for which Roche elects not to exercise its applicable option.

Prior to Roche's exercise of an option, we have the lead responsibility for drug discovery and preclinical development of all collaboration programs. In addition, we have the lead responsibility for the conduct of all Phase 1 clinical trials other than those Phase 1 clinical trials for any product in combination with Roche's portfolio of therapeutics, for which Roche will have the right to lead the conduct of such Phase 1 clinical trials. Pursuant to the Roche immunotherapy agreement, the parties share the costs of Phase 1 development for each collaboration program. In addition, Roche will be responsible for post-Phase 1 development costs for the licensed product for which it retains global commercialization rights, and we and Roche will share post-Phase 1 development costs for the licensed product for which we retain commercialization rights in the U.S.

We received an upfront cash payment of $45.0 million in March 2016 upon execution of the Roche immunotherapy agreement, and through December 31, 2021, we have achieved $23.5 million in milestone payments under this collaboration. Subject to the terms of the Roche immunotherapy agreement, as amended, in addition to upfront and milestone payments received through December 31, 2021, we are eligible to receive up to approximately $319.3 million in contingent option fees and milestone payments related to specified research, preclinical, clinical, regulatory and sales-based milestones. In addition, for any licensed product for which Roche retains worldwide commercialization rights, we will be eligible to receive tiered royalties ranging from low double-digits to high-teens on future net sales of the licensed product. For any licensed product for which we retain commercialization rights in the U.S., we and Roche will be eligible to receive tiered royalties ranging from mid-single-digits to low double-digits on future net sales in the other party's respective territories in which it commercializes the licensed product. The upfront cash payment and any payments for milestones, option fees and royalties are non-refundable, non-creditable and not subject to set-off.

Under the Roche immunotherapy agreement, each party has granted the other party specified intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the Roche immunotherapy agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the Roche immunotherapy agreement. Following Roche's exercise of its option with respect to the collaboration programs for which it will obtain worldwide rights, we will grant Roche an exclusive license under our intellectual property to develop and commercialize the licensed products generated through such collaboration program. Similarly, Roche will grant us an exclusive license under Roche's intellectual property to develop and commercialize licensed products in the U.S. for the collaboration programs on which we will retain rights in the U.S., with Roche receiving a license under our intellectual property to develop and commercialize such licensed products outside of the U.S.

Subject to the terms and conditions of the Roche immunotherapy agreement, we have agreed to work exclusively with Roche with respect to each collaboration target. We are not obligated to work exclusively with Roche within the field of cancer immunotherapy. In addition, subject to specified exceptions, Roche has a right of first negotiation in the event that we desire to grant any third party rights to develop or commercialize a licensed product for which we retain commercialization rights in the U.S. Roche's right of first negotiation will not apply in connection with a change of control of us, an assignment by us in accordance with the terms of the Roche immunotherapy agreement or certain agreements with contract research organizations, contract manufacturing organizations, academic institutions, not-for-profit third parties or distributors.

The Roche immunotherapy agreement will continue until the date when no royalty or other payment obligations are or will become due, unless earlier terminated in accordance with the terms of the Roche immunotherapy agreement. Prior to its exercise of its first option, Roche may terminate the Roche immunotherapy agreement at will, in whole or on a collaboration target-by-collaboration target basis, upon 120 days' prior written notice to us. Following its exercise of an option, Roche may terminate the Roche immunotherapy agreement at will, in whole, on a collaboration target-by-collaboration target basis, on a collaboration program-by-collaboration program basis or, if a licensed product has been commercially sold, on a country-by-country basis, (i) upon 120 days' prior written notice if a licensed product has not been commercially sold or (ii) upon 180 days' prior written notice if a licensed product has been commercially sold. Either party may terminate the Roche immunotherapy agreement for the other party's uncured material breach or insolvency and in certain other circumstances agreed to by the parties. In certain termination circumstances, we are entitled to retain specified licenses to be able to continue to exploit the licensed products.

Roche – Pralsetinib Collaboration

On July 13, 2020, we entered into a collaboration agreement, or the Roche pralsetinib collaboration agreement, with Roche pursuant to which we granted Roche exclusive rights to develop and commercialize pralsetinib worldwide, excluding the CStone territory, and a co-exclusive license in the U.S. to develop and commercialize pralsetinib. In addition, Roche has the right to opt in to a next-generation RET compound co-developed by Roche and us.

Under the Roche pralsetinib collaboration agreement, we received upfront cash payments of $775.0 million in the third quarter of 2020, including an upfront payment of $675.0 million and the $100.0 million equity investment by Roche described below. Through December 31, 2021, we have received $105.0 million in specified regulatory and commercialization milestones. In addition to the upfront and milestone payments received through December 31, 2021, we are eligible to receive up to $822.0 million in contingent payments, including specified development, regulatory and sales-based milestones for pralsetinib and any licensed product containing a next-generation RET compound.

In the U.S., we and Roche are working together to co-commercialize pralsetinib and will equally share responsibilities, profits and losses. In addition, we are eligible to receive tiered royalties ranging from high-teens to mid-twenties on annual net sales of pralsetinib outside the U.S., excluding the CStone territory, which we refer to as the Roche territory. We and Roche have also agreed to co-develop pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, as well as other solid tumors. We and Roche will share global development costs for pralsetinib at a rate of 45 percent for us and 55 percent for Roche up to a specified amount of aggregate joint development costs, after which our share of global development costs for pralsetinib will be reduced by a specified percentage. We and Roche will also share specified global development costs for any next-generation RET compound co-developed under the collaboration in a similar manner.

Unless earlier terminated in accordance with its terms, the Roche pralsetinib collaboration agreement will expire on a licensed product-by-licensed product basis (i) in the U.S. upon the expiration of the gross profit sharing term for such licensed product and (ii) outside the U.S. on a country-by-country basis at the end of the applicable royalty term for such licensed product. Roche may terminate the agreement in its entirety or on a licensed product-by-licensed product or country-by-country basis subject to certain notice periods. Either party may terminate the Roche pralsetinib collaboration agreement for the other party's uncured material breach or insolvency. Subject to the terms of the Roche pralsetinib collaboration agreement, effective upon termination of the agreement, we are entitled to retain specified licenses to be able to continue to exploit the licensed products.

In connection with the Roche collaboration agreement, on July 13, 2020, we also entered into a stock purchase agreement with Roche Holdings, Inc., or Roche Holdings, pursuant to which we issued and sold an aggregate of 1,035,519 of shares of common stock to Roche Holdings at a purchase price of $96.57 per share and received $100.0

million in the third quarter of 2020. The closing for a minority portion of the equity investment occurred following the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and other customary closing conditions.

CStone

On June 1, 2018, we entered into a collaboration and license agreement, or the CStone agreement, with CStone pursuant to which we granted CStone exclusive rights to develop and commercialize avapritinib, pralsetinib and fisogatinib, as well as certain back-up forms and certain other forms thereof, which we refer to collectively as the licensed products, in the CStone territory, either as a monotherapy or as part of a combination therapy. We will retain exclusive rights to the licensed products outside the CStone territory.

We received an upfront cash payment of $40.0 million, and through December 31, 2021, we have received $23.0 million in milestone payments under this collaboration. Subject to the terms of the CStone agreement, in addition to upfront and milestone payments received through December 31, 2021, we will be eligible to receive up to approximately $323.0 million in additional milestone payments, including $95.5 million related to development and regulatory milestones and $227.5 million related to sales-based milestones. In addition, CStone will be obligated to pay us tiered percentage royalties on a licensed product-by-licensed product basis ranging from the mid-teens to low twenties on annual net sales of each licensed product in the CStone territory, subject to adjustment in specified circumstances. CStone will be responsible for costs related to the development of the licensed products in the CStone territory, other than specified costs related to the development of fisogatinib as a combination therapy in the CStone territory that will be shared by us and CStone.

Pursuant to the terms of the CStone agreement, CStone is responsible for conducting all development and commercialization activities in the CStone territory related to the licensed products. Subject to specified exceptions, during the term of the CStone agreement, each party has agreed that neither it nor its affiliates will conduct specified development and commercialization activities in the CStone territory related to selective inhibitors of FGFR4, KIT, PDGFRA and RET. In addition, under the CStone agreement, each party has granted the other party specified intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the CStone agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the CStone agreement.

The CStone agreement will continue on a licensed product-by-licensed product and region-by-region basis until the later of (i) 12 years after the first commercial sale of a licensed product in a region in the CStone territory and (ii) the date of expiration of the last valid patent claim related to our patent rights or any joint collaboration patent rights for the licensed product that covers the composition of matter, method of use or method of manufacturing such licensed product in such region. Subject to the terms of the CStone agreement, CStone may terminate the CStone agreement in its entirety or with respect to one or more licensed products for convenience by providing written notice to us, and CStone may terminate the CStone agreement with respect to a licensed product for convenience at any time by providing written notice to us following the occurrence of specified events. In addition, we may terminate the CStone agreement under specified circumstances if CStone or certain other parties challenges our patent rights or any joint collaboration patent rights or if CStone or its affiliates do not conduct any material development or commercialization activities with respect to one or more licensed products for a specified period of time, subject to specified exceptions. Either party may terminate the CStone agreement for the other party's uncured material breach or insolvency. In certain termination circumstances, the parties are entitled to retain specified licenses to be able to continue to exploit the licensed products, and in the event of termination by CStone for our uncured material breach, we will be obligated to pay CStone a low single digit percentage royalty on a licensed product-by-licensed product on annual net sales of such licensed product in the CStone territory, subject to a cap and other specified exceptions.

Clementia

On October 15, 2019, we entered into a license agreement, or the Clementia agreement, with Clementia, a wholly-owned subsidiary of Ipsen S.A. Under the Clementia agreement, we granted an exclusive, worldwide, royalty-bearing license to Clementia to develop and commercialize BLU-782, an oral, highly selective investigational ALK2 inhibitor in clinical development for the treatment of FOP, as well as specified other compounds related to the BLU-782 program, which we refer to as the Clementia licensed products.

We received an upfront cash payment of $25.0 million in the fourth quarter of 2019, and through December 31, 2021, we have received $20.0 million in milestone payments under this license agreement. Subject to the terms of the Clementia agreement, in addition to the upfront and milestone payments received, we will be eligible to receive up to $490.0 million in development, regulatory and sales-based milestone payments for the Clementia licensed products. In addition, Clementia is obligated to pay to us royalties on aggregate annual worldwide net sales of Clementia licensed products at tiered percentage rates ranging from the low- to mid-teens, subject to adjustment in specified circumstances under the Clementia agreement, and to purchase specified manufacturing inventory from our company.

Under the terms of the Clementia agreement, we were responsible for specified activities during a transition period, which has been completed, and Clementia is responsible for conducting all development and commercialization activities related to the Clementia licensed products, including the design, timing and conduct of any Phase 2 clinical trial evaluating BLU-782 for the treatment of FOP.

During the term of the agreement, we have agreed not to exploit any compound covered by the licensed patents for the treatment of FOP or multiple osteochondromas, or MO. In addition, with respect to any small molecule compound not covered by the licensed patents, we have agreed not to research, develop or manufacture any small molecule compound for the treatment of FOP or MO for a period of five years from the effective date of the Clementia agreement and not to commercialize any small molecule compound for the treatment of FOP or MO for a period of seven years from the effective date of the Clementia agreement.

Unless earlier terminated in accordance with the terms of the Clementia agreement, the agreement will expire on a country-by-country, licensed product-by-licensed product basis on the date when no royalty payments are or will become due. Clementia may terminate the agreement at any time on or after October 15, 2021 upon at least 12 months' prior written notice to us. Either party may terminate the agreement for the other party's uncured material breach or insolvency and in certain other circumstances agreed to by the parties. In certain termination circumstances, we are entitled to retain specified licenses to be able to continue to exploit the Clementia licensed products.

Zai Lab

On November 8, 2021, we entered into a license agreement, or the Zai Lab agreement, with Zai Lab. Under the Zai Lab agreement, we granted an exclusive license for the development and commercialization of BLU-701 and BLU-945 for the treatment of EGFR-driven NSCLC in Greater China, including Mainland China, Hong Kong, Macau and Taiwan.

We received an upfront cash payment of $25.0 million in the fourth quarter of 2021. Subject to the terms of the Zai Lab agreement, in addition to the upfront payment received, we will be eligible to receive up to $590.0 million in potential development, regulatory and sales-based milestone payments, and tiered royalties on a product-by-product basis ranging from the low-teens to mid-teens on annual net sales of BLU-701 and BLU-945 in Greater China, subject to adjustment in specified circumstances under the Zai Lab agreement.

Under the terms of the agreement, Zai Lab will be responsible for all the development costs for BLU-701 and BLU-945 occurring in Greater China.

Mergers & Acquisitions

Lengo Therapeutics, Inc.

On November 27, 2021, we entered into an Agreement and Plan of Merger, or the Merger Agreement, with Pavonis Merger Subsidiary, Inc., a Delaware corporation and our wholly-owned subsidiary, or Merger Sub, Lengo Therapeutics, Inc., a Delaware corporation, or Lengo, and Fortis Advisors LLC, a Delaware limited liability company, as the representative of the Lengo Securityholders (as defined below). On December 30, 2021, we completed the merger of Merger Sub with and into Lengo, with Lengo continuing as the surviving corporation and our wholly-owned subsidiary, or the Closing. Upon Closing we acquired Lengo's lead compound LNG-451, now known as BLU-451, which is in development for the treatment of EGFR exon 20 insertion-positive NSCLC, in addition to undisclosed preclinical precision oncology programs and research tools, including a catalog of covalent, highly brain penetrant kinase inhibitors that we plan to add

to our proprietary compound library to further enable future drug discovery efforts.

Upon Closing, we paid upfront merger consideration of $250.0 million in cash, or the Upfront Merger Consideration, to Lengo stockholders and option holders, or collectively, the Lengo Securityholders. The Merger Agreement also provided that we shall pay future contingent cash milestone payments of up to $215.0 million in the aggregate to the Lengo Securityholders upon the achievement of specified regulatory approval and sales milestones. The Upfront Merger Consideration is subject to customary net indebtedness, transaction expenses, and other adjustments, as set forth in the Merger Agreement.

The Merger Agreement also provided that approximately $25.0 million of the Upfront Merger Consideration was placed into a third party escrow account, or the Indemnification Escrow, to secure the Lengo Securityholders' obligations to indemnify us for certain matters, including breaches of representations and warranties, covenants included in the Merger Agreement, payments made by us to dissenting stockholders, specified tax claims, excess parachute claims, purchase price adjustments, and other customary matters, subject to certain specified limitations, including, among other things, limitations on the period during which we may make certain claims for indemnification and limitations on the amounts for which the Lengo Securityholders may be liable.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our drug and drug candidates, as well as our core technologies, including our novel target discovery engine, our proprietary compound library, and other know-how; to operate without infringing on the proprietary rights of others; and to prevent others from infringing our proprietary or intellectual property rights. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing U.S., international and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

We file patent applications directed to our marketed drugs AYVAKIT®/AYVAKYT®, GAVRETO® and our drug candidates in an effort to establish intellectual property positions regarding these new chemical entities as well as uses of these new chemical entities in the treatment of diseases and to other technologies, including formulations, solid state forms, manufacturing processes, patient selection markers and diagnostic discoveries that may be useful with our drugs and drug candidates. We also file patent applications directed to novel fusions that we have discovered through our target discovery engine and the use of these fusions in diagnosing and treating disease. As of January 31, 2022, we own or have licensed 37 issued U.S. patents, 18 pending U.S. non-provisional patent applications, 21 pending U.S. provisional applications, 62 issued foreign patents, 147 foreign pending patent applications, and 12 pending Patent Cooperation Treaty, or PCT, international patent applications related to our most advanced programs and platform technology. The foreign issued patents and pending patent applications are in a number of jurisdictions, including Argentina, Australia, Brazil, Canada, China, the European Union, Gulf Cooperation Council, Hong Kong, Israel, Japan, South Korea, Macao, Mexico, New Zealand, Philippines, Russia, Singapore, South Africa, and Taiwan. Our issued patents and pending patent applications pertain to our marketed drugs AYVAKIT® and GAVRETO® and drug candidates, including fisogatinib, BLU-263, BLU-945, BLU-701, BLU-451, and BLU-222 as well as novel recurrent fusions.

We file trademarks to protect our products. Typically, we file trademark applications in the U.S., Europe, and elsewhere in the world as appropriate. In addition to multiple pending trademark applications in the U.S. and other major countries, we have registered trademarks, including but not limited to AYVAKIT and GAVRETO in the U.S. and to AYVAKYT in the EU.

The intellectual property portfolios for our approved drugs and most advanced programs as of January 31, 2022 are summarized below. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, and by patent offices in other countries are often significantly narrowed by the time they issue, if they issue at all. We expect this to be the case with respect to our pending patent applications referred to below. In addition to patents and trademarks for our drug products, we seek to obtain all available regulatory exclusivities for our marketed products, including data and orphan exclusivities in the relevant jurisdictions.

KIT and PDGFRA Program—AYVAKIT/AYVAKYT (avapritinib) and BLU-263

The intellectual property portfolio for our KIT and PDGFRA program contains patent applications directed to compositions of matter for avapritinib, BLU-263 and analogs thereof, compositions of matter for KIT and PDGFRA inhibitors with different compound families, as well as solid forms, methods of use and manufacture. As of January 31, 2022, the portfolio contains 12 issued U.S. patents, 16 issued foreign patents, including one European patent validated in 38 countries, four pending U.S. non-provisional patent applications, three pending U.S. provisional applications, four pending PCT international patent applications and 51 pending foreign patent applications. The patents that have issued or will issue covering our KIT and PDGFRA program will have a statutory expiration date between 2034 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

RET Program—GAVRETO (pralsetinib)

The intellectual property portfolio for our RET program contains patent applications directed to compositions of matter for pralsetinib and analogs thereof, compositions of matter for RET inhibitors with different compound families, as well as solid forms, formulations, methods of use and manufacture. As of January 31, 2022, the portfolio contains seven issued U.S. patents, five pending U.S. non-provisional patent applications, two U.S. provisional patent applications, three pending PCT international applications, 58 pending foreign patent applications and nine issued foreign patents. The patents that have issued or will issue covering our RET program will have a statutory expiration date between 2036 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

FGFR4 Program — Fisogatinib

The intellectual property portfolio for our FGFR4 program contains patent applications directed to compositions of matter for fisogatinib and analogs and compositions of matter for FGFR4 inhibitors with different compound families as well as methods of use. As of January 31, 2022, the patent portfolio for our FGFR4 program, including fisogatinib contains nine issued U.S. patents, two pending U.S. non-provisional patent applications, one pending PCT international application, 21 pending foreign patent applications and 29 issued foreign patents. The patents that have issued or will issue covering our FGFR4 program will have a statutory expiration date between 2033 and 2040. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

EGFR Program

The intellectual property portfolio for our EGFR program contains patent applications directed to compositions of matter for BLU-945, BLU-701, BLU-451 and analogs thereof, compositions of matter for EGFR inhibitors with different compound families, as well as solid forms, formulations, methods of use and manufacture. As of January 31, 2022, we owned one issued U.S. patent, one pending U.S. non-provisional patent application, 13 pending U.S. provisional applications, four pending PCT international patent applications and 14 pending foreign patent applications and two issued foreign patents, including one European patent validated in 6 countries directed to our EGFR program, including BLU-945, BLU-701, and BLU-451. The patents that have issued or will issue covering our EGFR program will have a statutory expiration date between 2034 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

CDK2 Program

The intellectual property portfolio for our CDK2 program contains patent applications directed to compositions of matter for CDK2 inhibitors for BLU-222 and analogs thereof, compositions of matter for CDK2 inhibitors with different compound families, as well as methods of use. As of January 31, 2022, we owned three pending U.S. provisional applications. The patents that will issue covering our CDK2 program will have a statutory expiration date of 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

Platform

The intellectual property portfolio directed to our platform includes patent applications directed to novel gene fusions and the uses of these fusions for detecting and treating conditions implicated with these fusions. As of January 31, 2022, the patent portfolio directed to our platform contains eight issued U.S. patents, six pending U.S. non-provisional patent applications, three pending European Union patent applications and six issued European patents. Any U.S. or ex-U.S. patent issuing from the pending applications directed to this technology, if issued, will have statutory expiration dates ranging from 2034 to 2035.

Other Considerations

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the U.S., the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the U.S., a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See "*— Government Regulation — U.S. Patent Term Restoration and Marketing Exclusivity*" below for additional information on such exclusivity. In the future, if applicable and when our drug candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our drug, drug candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, our pending patent applications, and any patent applications that we may in the future file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the U.S. that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a drug or drug candidate we may develop, it is possible that, before any of our approved drugs or drug candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators, third-party service providers, and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees. We have also executed agreements requiring assignment of inventions with selected scientific advisors, consultants and collaborators. The confidentiality agreements we enter into are designed to protect our proprietary information and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that these agreements will afford us adequate protection of our intellectual property and proprietary information rights.

With respect to the building of our proprietary compound library, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to our discovery platform, these trade secrets and know-how will over time be disseminated within the industry through independent development and public presentations describing the methodology.

Competition

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

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address inhibition of kinases in cancer and other rare diseases. There are other companies working to develop therapies in the field of kinase inhibition for cancer and other diseases. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

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

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any drugs that we or our collaborators may develop. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we or our collaborators are able to enter the market. The key competitive factors affecting the success of our drugs and our current or future drug candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostic tests in guiding the use of related therapeutics, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our approved drugs and drug candidates, to the extent they receive marketing approval in the future for indications for which we are currently conducting or planning clinical trials, compete with or will compete with the drugs discussed below and will likely compete with other drugs that are currently in development.

SM

AYVAKIT/AYVAKYT faces competition for advanced SM from Novartis AG's midostaurin and imatinib, and may face competition from drug candidates in development, including that being developed by Cogent Biosciences, Inc. We are developing avapritinib for non-advanced SM, and we are developing BLU-263 for the treatment of non-advanced SM and other mast cell disorders. If avapritinib and BLU-263 are approved for non-advanced SM, they may face competition from drug candidates in development, including those being developed by AB Science S.A., Allakos Inc. and Cogent Biosciences, Inc.

RET-Altered Cancers

GAVRETO faces competition for RET fusion-positive NSCLC and RET-altered thyroid carcinoma, including MTC, from Eli Lilly and Company's selpercatinib. If pralsetinib receives marketing approval for patients with other solid tumors, it will also face competition from selpercatinib for these additional indications. In addition, pralsetinib may face competition from other drug candidates in development for RET-altered cancers, including those being developed by AstraZeneca plc, Boston Pharmaceuticals, Inc., Eisai Inc., Exelixis, Inc., GlaxoSmithKline plc, Mirati Therapeutics, Inc., Novartis AG, Pfizer Inc. Roche, Stemline Therapeutics, Inc., and Turning Point Therapeutics, Inc., as well as

several approved multi-kinase inhibitors with RET activity being evaluated in clinical trials, including alectinib, apatinib, cabozantinib, dovitinib, lenvatinib, sorafenib, sunitinib and vandetinib.

GIST

AYVAKIT/AYVAKYT may face competition from drug candidates in development for PDGFRA-driven GIST, including those being developed by AB Science S.A., ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AROG Pharmaceuticals, Inc., AstraZeneca plc, Celldex Therapeutics, Inc., Cogent Biosciences, Inc., Deciphera Pharmaceuticals, LLC, Exelixis, Inc., Ningbo Tai Kang Medical Technology Co. Ltd. and Xencor, Inc.

EGFR-Mutated NSCLC

We are developing BLU-701 and BLU-945 for treatment-resistant EGFR-mutated NSCLC, which, if approved, will face competition from AstraZeneca plc's osimertinib and almonertinib, which is under collaboration between Jiangsu Hansoh Pharmaceutical Group Co., Ltd. and EQRX, Inc. and approved in China. In addition, BLU-701 and BLU-945 may face competition from drug candidates in development for EGFR-mutated NSCLC, including those being developed by Allist Pharmaceuticals, Arrivent Biopharma, Inc., Betta Pharmaceuticals, Black Diamond Therapeutics, Inc., Boehringer Ingelheim RCV GmbH & Co KG, Bridge Biotherapeutics, Inc., Centessa Pharmaceuticals plc, C4 Therapeutics, Inc., Chia Tai Tianqing Pharmaceutical Group, Daiichi Sankyo Company, Limited, Janssen Pharmaceuticals, Inc., Kanaph Therapeutics and Theseus Pharmaceuticals, Inc.

We are developing BLU-451 for EGFR exon 20 insertion-positive NSCLC, which, if approved, will face competition from Janssen Pharmaceuticals, Inc. and Takeda Pharmaceuticals. In addition, BLU-451 may face competition from drug candidates in development for EGFR exon 20 insertion-positive NSCLC, including those being developed by Abbisko Therapeutics Co., Ltd., Bayer AG, Black Diamond Therapeutics, Inc., Centessa Pharmaceuticals plc, Cullinan Oncology, Inc., Daiichi Sankyo Company, Limited, Dizal Pharmaceutical Co. Ltd., Shenzhen Forward Pharmaceutical Co., Ltd., Shanghai Junshi Biosciences Co., Ltd., Oric Pharmaceuticals, Inc. and Scorpion Therapeutics, Inc.

Cyclin E Aberrant Cancers

We are developing BLU-222 for cyclin E aberrant cancers, which, if approved, will face competition from indication-specific therapies such as Genentech's bevacizumab, AstraZeneca and Merck's olaparib, Clovis Oncology's rucaparib, GSK's niraparib, Merck's pembrolizumab, and Eisai's lenvatinib. In addition, BLU-222 may face competition from drug candidates in development for cyclin E aberrant cancers, including those being developed by ARC Therapeutics, Inc., Cedilla Therapeutics, Inc., Cyclacel Pharmaceuticals Inc., Monte Rosa Therapeutics, Inc., Nuvation Bio, Inc., Regor Therapeutics Inc., Pfizer Inc., AstraZeneca plc, Zentalis Pharmaceuticals, Inc. and Repare Therapeutics, Inc.

Advanced Cancers

We are developing BLU-852 for advanced cancers susceptible to MAP4K1 inhibition, which, if approved, will face competition from immuno-oncology products, including those developed by Bristol-Myers Squibb Company, Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., Sanofi S.A., and AstraZeneca plc. In addition, BLU-852 may face competition from drug candidates in development for advanced cancers susceptible to MAP4K1 inhibition, including those being developed by Treadwell Therapeutics, Inc., BeiGene, Ltd., Nimbus Therapeutics, LLC and MingMed Biotechnology Co., Ltd.

Commercialization

As a fully-integrated, global precision therapy company focused on discovering, developing and commercializing a portfolio of precision therapies, our vision is to bring life-changing precision therapies to as many patients with cancer and blood disorders as possible. We have established our own commercial organization in the U.S. and Europe in connection with our commercial launches of AYVAKIT and GAVRETO in the U.S. and AYVAKYT in

Europe. We have also entered into collaborations with our partners, including CStone and Roche, for global commercialization activities for AYVAKIT/AYVAKYT and GAVRETO in their respective territories. We are continuing to expand our commercialization capabilities and to build our distribution capabilities to accelerate global adoption of our approved drugs and to prepare for additional planned commercial launches with an initial focus on the U.S. and Europe.

We believe our portfolio strategy focused on genomically defined cancers and blood disorders will allow us to efficiently commercialize approved drugs in the U.S. and Europe initially and worldwide longer-term, using a small and highly specialized sales force similar to those of other rare disease companies. We may also evaluate opportunities to establish collaborations with pharmaceutical companies to leverage their capabilities to maximize the potential of our pipeline from time to time.

Manufacturing and Supply

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our drug candidates for preclinical and clinical testing, as well as for commercial manufacture of any drug we may commercialize. To date, we have obtained materials for avapritinib, pralsetinib, fisogatinib, BLU-263, BLU-945, BLU-701, BLU-222 and BLU-451 for our ongoing and planned clinical testing from third-party manufacturers. We obtain our supplies from these manufacturers on a purchase order basis and do not have a long-term supply arrangement in place. Although we have negotiated manufacturing agreements with certain venders for the commercial supply of AYVAKIT/AYVAKYT and GAVRETO, we may also obtain our supplies for these approved drugs from these manufacturers on a purchase order basis from time to time. We rely primarily on single-source third-party suppliers to manufacture and supply our drugs and may from time to time explore opportunities to identify and qualify additional manufacturers to provide the API, drug substance and drug products.

All of our approved drugs and drug candidates are compounds of low molecular weight, generally called small molecules. They can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale-up and does not require unusual equipment in the manufacturing process. We expect to continue developing drug candidates that can be produced cost-effectively at contract manufacturing facilities.

Under the terms of our agreements related to the development and commercialization of companion diagnostic tests, third parties are responsible for the commercialization of companion diagnostic tests, including for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation and pralsetinib in order to identify NSCLC patients with RET fusions. We generally expect to rely on third parties for the manufacture of any other companion diagnostic tests we may seek to develop.

Government Regulation

Government authorities in the U.S. at the federal, state and local level and in other countries extensively regulate, among other things, the research and clinical development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing, and export and import of drug products, such as those we are developing. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable regulatory requirements at any time during the product development process, approval process or after approval may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the regulatory authority’s refusal to approve pending applications, withdrawal of an approval, clinical holds, untitled or warning letters, voluntary product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution, injunctions, debarment, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

U.S. Drug Development

In the U.S., the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. Our drug candidates must be approved by the FDA through the NDA process before they may be legally marketed in the U.S. The process required by the FDA before a drug may be marketed in the U.S. generally involves the following:

- completion of extensive nonclinical tests, sometimes referred to as preclinical laboratory tests, animal studies and formulation studies performed in accordance with applicable regulations, including the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be actively maintained, including by submitting 15- or 7-day safety reports and annual safety reports;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for its proposed indication;
- submission to the FDA of an NDA for a new drug;
- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;
- review of the drug candidate by an FDA advisory committee, where appropriate or if applicable;
- payment of user fees for FDA review of the NDA (unless a fee waiver applies);
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the API and finished drug product are produced to assess compliance with the FDA's current good manufacturing practice, or cGMP, requirements, where appropriate or if applicable;
- potential FDA audit of the preclinical study sites and/or clinical trial sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the U.S.

The data required to support an NDA is generated in two distinct development stages: preclinical and clinical. For new chemical entities, the preclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the preclinical tests must comply with federal regulations, including GLPs, where applicable. The sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the preclinical data, general investigational plan and the protocol(s) for human trials. The IND becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, 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 could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers and/or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial

sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Failure to timely register a clinical trial or to submit study results to such public registries can give rise to civil monetary penalties and also prevent a non-compliant party from receiving future grant funds from the federal government.

Clinical trials are generally conducted in three sequential phases that may overlap or be combined, known as Phase 1, Phase 2 and Phase 3 clinical trials. Phase 1 clinical trials for oncology indications generally involve a small number of disease-affected patients who are treated with the drug candidate in escalating dose cohorts. The primary purpose of these clinical trials is to determine the MTD, or a recommended dose if the MTD is not achieved, assess the pharmacokinetic, or PK, profile, pharmacologic action, side effect tolerability and safety of the drug. Phase 1 clinical trials for oncology indications may also evaluate preliminary evidence of clinical activity. Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further PK and PD information is collected, as well as identification of possible AEs and safety risks and preliminary evaluation of efficacy. Phase 3 clinical trials generally involve large numbers of patients (from several hundred to several thousand subjects) at multiple sites, in multiple countries and are designed to provide the data necessary to demonstrate the efficacy of the drug for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the drug and provide an adequate basis for physician labeling. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a drug during marketing. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA. However, in settings of rare diseases and genetically-driven cancers, regulatory flexibility is given on a case-by-case basis.

Post-approval trials, sometimes 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 patients in the intended therapeutic indication. In certain instances, FDA may mandate the performance of Phase 4 clinical trials as post-marketing commitments or requirements.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse reactions, any finding from other clinical studies, tests in laboratory animals, or *in vitro* testing that suggests a significant risk for human subjects, or any clinically important increase in the rate 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, if at all. The FDA or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. In addition, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, cGMPs impose extensive procedural, substantive and recordkeeping requirements to ensure and preserve the long-term stability and quality of the final drug product. In addition, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA Review Process

Following trial completion, trial data are analyzed to assess safety and efficacy. The results of preclinical studies and clinical trials are then submitted to the FDA as part of an NDA, along with proposed labeling for the drug and information about the manufacturing process and facilities that will be used to ensure drug quality, results of analytical testing conducted on the chemistry of the drug, and other relevant information. The NDA is a request for approval to market the drug and must contain adequate evidence of safety and efficacy, which is demonstrated by extensive preclinical and clinical testing. The application includes both negative or ambiguous results of preclinical studies and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a use of a drug, 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 the investigational drug product to the satisfaction of the FDA. FDA approval of an NDA must be obtained before a drug may be offered for sale in the U.S.

In addition, under the Pediatric Research Equity Act, or PREA, as amended, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fiscal year 2021 fee schedule, effective through September 30, 2021, the user fee for an application requiring clinical data, such as an NDA, is $2,875,842. PDUFA also imposes an annual prescription drug product program fee for human drugs ($336,432 for the current fiscal year). Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. In addition, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, for a new molecular entity the FDA has ten months from the filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the filing date for a priority NDA. The submission of a major amendment at any time during the review cycle may extend the PDUFA action date by up to three months. Only one extension can be given per review cycle. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed drug is safe and effective for its intended use, and whether the drug is being manufactured in accordance with cGMP to assure and preserve the drug's identity, strength, quality and purity. The FDA may refer applications for novel drugs or drug candidates that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and us during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new drug to determine whether they comply with cGMPs. The FDA will not approve the drug unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the drug within required specifications. In addition, before approving an NDA, the FDA may also audit data from clinical trials by inspecting the sponsor or clinical trial sites to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities where the drug product and/or its API will be produced, it may issue an approval letter or a Complete Response Letter or defer action on an application where required inspections cannot be conducted due to the COVID-19 pandemic. An approval

letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application or request a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the U.S. and we may encounter significant difficulties or costs during the review process. If a drug receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the drug. Further, the FDA may require that certain contraindications, warnings or precautions be included in the drug labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved drugs. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved drugs that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of drugs. Drug approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval, priority review and breakthrough therapy designation, that are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life-threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures. To be eligible for fast track designation, the FDA must determine, based on the request of a sponsor, that a drug is intended to treat a serious or life-threatening disease or condition and based on preclinical or preliminary clinical data demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors.

The FDA may give a priority review designation to drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six- and ten-month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

In addition, drugs 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 and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on

irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures.

Moreover, a sponsor can request designation of a drug candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval and priority review. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Furthermore, fast track designation, priority review, accelerated approval and breakthrough therapy designation, do not change the standards for approval and may not ultimately expedite the development or approval process.

Pediatric Trials

A sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include an outline of the pediatric study or studies that 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. FDA and the sponsor must reach agreement on the PSP. 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 preclinical studies, early phase clinical trials, and/or other clinical development programs.

Post-Marketing Requirements

Following approval of a new drug, a pharmaceutical company and the approved drug are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the drug, providing the regulatory authorities with updated safety and efficacy information, drug sampling and distribution requirements, and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling, which is known as "off-label use", and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. There are also limitations on industry-sponsored scientific and educational activities. Modifications or enhancements to the drug or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process. Any distribution of prescription drugs and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the U.S., once a drug is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that drugs be manufactured in specific approved facilities and in accordance with cGMP. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our drugs in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production

and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute drugs manufactured, processed or tested by them. Discovery of problems with a drug after approval may result in restrictions on a drug, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the drug from the market, and may require substantial resources to correct.

The FDA also may require post-approval commitments, which may include testing that are sometimes referred to as post-marketing studies or clinical studies, risk minimization action plans and post-marketing surveillance to monitor the effects of an approved drug or place conditions on an approval that could restrict the distribution or use of the drug. Discovery of previously unknown problems with a drug or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, untitled or warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a drug's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. The distribution of pharmaceutical drugs is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical drugs.

Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our drugs under development.

Other Regulatory Matters

Manufacturing, sales, promotion and other activities following drug approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the U.S., the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Drug Enforcement Administration for controlled substances, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the U.S., sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act. If drugs are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Drugs must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The failure to comply with regulatory requirements and changes to regulatory requirements subjects firms to possible legal or regulatory action. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or efficacy of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the

time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the U.S. to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full 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. Orphan drug exclusivity, as described below, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the U.S. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued “Written Request” for such a trial.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the U.S., or if it affects more than 200,000 individuals in the U.S., there is no reasonable expectation that the cost of developing and marketing the drug for this type of disease or condition will be recovered from sales in the U.S. In the EU, the European Commission, after receiving the opinion of the EMA’s Committee for Orphan Medicinal Products, or COMP, grants medicinal product designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU Community. In addition, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug or biological product.

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 receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

In the EU, orphan medicinal product designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following drug or biological product approval. This period may be reduced to six years if the medicinal product designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Rare Pediatric Disease Designation and Priority Review Vouchers

Under the FDCA, the FDA incentivizes the development of drugs products that meet the definition of a "rare pediatric disease," defined to mean a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making in the United States a drug product for such disease or condition will be received from sales in the United States of such drug product. The sponsor of a product candidate for a rare pediatric disease may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug product application after the date of approval of the rare pediatric disease drug product, referred to as a priority review voucher, or PRV. A sponsor may request rare pediatric disease designation from the FDA prior to the submission of its NDA. A rare pediatric disease designation does not guarantee that a sponsor will receive a PRV upon approval of its NDA. Moreover, a sponsor who chooses not to submit a rare pediatric disease designation request may nonetheless receive a PRV upon approval of their marketing application if they request such a voucher in their original marketing application and meet all of the eligibility criteria. If a PRV is received, it may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with the potential for PRVs to be granted through September 30, 2026.

Regulation of Diagnostic Tests

We expect that our drug candidates may require use of a diagnostic to identify appropriate patient populations for our products. These diagnostics, often referred to as companion diagnostic tests, are medical devices, often *in vitro* devices, which provide information that is essential for the safe and effective use of a corresponding drug. For example, we have entered into agreements with third parties to develop and commercialize companion diagnostic tests, including for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation and pralsetinib in order to identify NSCLC patients with RET fusions. 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, establishment registration and device listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval. We expect that any companion diagnostic test developed for our drug candidates will utilize the PMA pathway.

PMA applications must be supported by valid scientific evidence, which typically requires extensive data, including technical, preclinical, clinical and manufacturing data, to demonstrate to the FDA's satisfaction the safety and effectiveness of the device. For diagnostic tests, a PMA application typically includes data regarding analytical and clinical validation studies. As part of its review of the PMA, the FDA will conduct a pre-approval inspection of the manufacturing facility or facilities to ensure compliance with the Quality System Regulation, or QSR, which requires manufacturers to follow design, testing, control, documentation and other quality assurance procedures. FDA review of an initial PMA may require several years to complete. If the FDA evaluations of both the PMA application and the manufacturing facilities are favorable, the FDA will either issue an approval letter or an approvable letter, which usually contains a number of conditions that must be met in order to secure the final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards is not maintained or problems are identified following initial marketing.

On August 6, 2014, the FDA issued a final guidance document addressing the development and approval process for "In Vitro Companion Diagnostic Devices." According to the guidance, for novel drugs such as our drug candidates, a companion diagnostic test device and its corresponding drug should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling. The guidance also explains that a companion diagnostic test device used to make treatment decisions in clinical trials of a drug generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption, or IDE, regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a drug are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the study plan and subjects, a sponsor may seek to submit an IND alone, or both an IND and an IDE.

In the European Economic Area, or EEA (which is comprised of the Member States of the EU plus Norway, Iceland and Liechtenstein), *in vitro* diagnostic medical devices are currently required to conform with the general safety and performance requirements of the E.U. Directive on *in vitro* diagnostic medical devices (Directive No 98/79/EC, as amended), however the new in-vitro diagnostics Regulation (Regulation (EU) 2017/746) will apply from 26 May 2022. Until then, manufacturers can opt to place in-vitro diagnostic devices on the market under Directive 98/79/EC or under the new Regulation if they fully comply with it. To demonstrate compliance with the general safety and performance requirements, the manufacturer must undergo a conformity assessment procedure. The conformity assessment varies according to the type of medical device and its classification. For low-risk devices, the conformity assessment can be carried out internally, but for higher risk devices it requires the intervention of an accredited EU Notified Body. If successful, the conformity assessment concludes with the drawing up by the manufacturer of an EC Declaration of Conformity entitling the manufacturer to affix the CE mark to its products and to sell them throughout the EU.

European Drug Development

In the European Union, our future drugs may also be subject to extensive regulatory requirements. As in the U.S., medicinal products can only be marketed if a marketing authorization from the competent regulatory agencies has been obtained.

Clinical Trial Approval

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, or the Clinical Trials Regulation, which replaced the current Clinical Trials Directive 2001/20/EC on 31 January 2022. The Clinical Trials Regulation is directly applicable in all EU Member States meaning no national implementing legislation in each EU Member State is required. It overhauls the current system of approvals for clinical trials in the EU. Specifically, the new legislation aims at simplifying and streamlining the approval of clinical trials in the European Union. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications.

European Drug Review and Approval

In the UK and the EU, medicinal products can only be commercialized after obtaining a marketing authorization, or MA. There are two types of marketing authorizations:

The centralized MA, which is issued by the European Commission through the centralized procedure, based on the opinion of the CHMP of the EMA and which is valid throughout the entire territory of the EU, and in the additional Member States of the European Economic Area (Iceland, Liechtenstein and Norway). The centralized procedure is mandatory for certain types of products, including medicines produced by certain biotechnological processes, advanced therapy medicinal products (gene-therapy, somatic cell-therapy or tissue-engineered medicines), products designated as orphan medicinal products, and products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EU, or for

drugs that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EU and only cover their respective territory, are available for products not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in a Member State of the EU, this national MA can be recognized in another Member State through the mutual recognition procedure. If the product has not received a national MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the reference member state, or RMS.

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

Now that the UK (which comprises Great Britain and Northern Ireland) has left the EU, Great Britain will no longer be covered by centralized MAs (under the Northern Ireland Protocol, centralized MAs will continue to be recognized in Northern Ireland). All medicinal products with a current centralized MA were automatically converted to Great Britain MAs on January 1, 2021. For a period of two years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain MA. A separate application will, however, still be required.

European Pediatric Investigation Plan

In the EU, MAAs for new medicinal products have to include the results of studies conducted in the pediatric population, in compliance with a pediatric investigation plan, or PIP, agreed with the EMA's Pediatric Committee, or PDCO. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which marketing authorization is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when this data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. If a marketing authorization is obtained and trial results are included in the product information, even when negative, the product is eligible for six-months' supplementary protection certificate extension. In the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

European Data and Market Exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a biosimilar or generic application for eight years, after which a biosimilar or generic marketing authorization can be submitted, and the innovator's data may be referenced, but not marketed for two years. The overall ten-year period will be extended to a maximum of 11 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.

European Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish: that (1) the product 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 (5) in ten thousand (10,000) persons in the EU when the application is made, or (b) it is unlikely that the product, without the benefits derived from orphan status, would generate sufficient return in the EU to justify the necessary investment in its development; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Products receiving orphan designation in the EU can receive ten years of market exclusivity, during which time no "similar medicinal product" may be placed on the market. 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.

However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, 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.

Regulatory Requirements After a Marketing Authorization has been Obtained

In case an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured. These rules can impose post-authorization studies and additional monitoring obligations.
- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

The aforementioned EU rules are generally applicable in the EEA, which consists of the EU Member States, plus Iceland, Liechtenstein and Norway.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit, and the UK formally left the EU on January 31, 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on December 31, 2020. However, the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore currently aligns with EU regulations, however it is possible that these regimes will diverge in future now that Great Britain's regulatory

system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation.

Rest of the World Regulation

For other countries outside of the European Union and the U.S., such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, drug licensing, pricing and reimbursement vary from country to country. In all cases the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Data Privacy and Security Laws

Pharmaceutical companies may be subject to U.S. federal and state health information privacy, security and data breach notification laws, which may govern the collection, use, disclosure and protection of health-related and other personal information. State laws may be more stringent, broader in scope or offer greater individual rights with respect to protected health information, or PHI, than the federal Health Insurance Portability and Accountability Act of 1996, as amended, and its implanting regulations, which are collectively referred to as HIPAA, and state laws may differ from each other, which may complicate compliance efforts. Entities that are found to be in violation of HIPAA as the result of a breach of unsecured PHI, a complaint about privacy practices or an audit by the Department of Health and Human Services, or HHS, may be subject to significant civil, criminal and administrative fines and penalties and/or additional reporting and oversight obligations if required to enter into a resolution agreement and corrective action plan with HHS to settle allegations of HIPAA non-compliance.

In addition to federal regulation, many states have begun to focus on efforts to regulate privacy and data security. For example, in California the California Consumer Protection Act, or CCPA, which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. While clinical trial data and information governed by HIPAA are currently exempt from CCPA, other personal information that we process may be subject to the CCPA and possible changes to the CCPA may broaden its scope.

EEA Member States, the UK, Switzerland and other jurisdictions have also adopted data protection laws and regulations, which impose significant compliance obligations. In the EEA and the UK, the collection and use of personal data, including clinical trial data, is governed by the provisions of the General Data Protection Regulation, or GDPR. The GDPR, together with national legislation, regulations and guidelines of the EEA Member States, the UK and Switzerland governing the processing of personal data, impose strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting. In particular, these obligations and restrictions concern the consent of the individuals to whom the personal data relates, the information provided to the individuals, the transfer of personal data out of the EEA, the UK or Switzerland, data breach notifications, security and confidentiality, responding and handling data subject rights, ensuring appropriate assessments are carried out on processing operations and documented. Under these laws data protection authorities can impose substantial potential fines for breaches of the data protection obligations. European data protection authorities may interpret the GDPR and national laws differently and impose additional requirements, which add to the complexity of processing personal data in or from the EEA, UK or Switzerland. Guidance on implementation and compliance practices are often updated or otherwise revised.

Coverage and Reimbursement

Sales of our drugs will depend, in part, on the extent to which our drugs will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. 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 drug is approved, sales of the drug 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 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. The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our drug and drug candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Further, due to the ongoing COVID-19 pandemic, millions of individuals have lost or will be losing employer-based insurance coverage, which may adversely affect our ability to commercialize our drugs.

These third-party payors are increasingly reducing or restricting reimbursements for medical drugs and services. In addition, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic drugs. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our drug candidates, if approved, or a decision by a third-party payor to not cover our drug candidates could reduce physician usage of such drugs and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for drugs for which we receive marketing approval. Any negotiated prices for our drugs covered by a Part D prescription drug plan may be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012

by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our drug candidates, if any such drug or the condition that they are intended to treat is the subject of a trial. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's drug could adversely affect the sales of our drug candidate. If third-party payors do not consider our drugs to be cost-effective compared to other available therapies, they may not cover our drugs after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our drugs on a profitable basis.

The Affordable Care Act has had a significant impact on the health care industry. The Affordable Care Act expanded coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, the Affordable Care Act, among other things, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

In addition, other legislative changes have been proposed and adopted in the U.S. since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, included aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. Following the temporary suspension, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.

In March 2010, the Affordable Care Act became law in the United States. The goal of the Affordable Care Act is to reduce the cost of healthcare and substantially change the way healthcare is financed by both governmental and private insurers. The Affordable Care Act, among other things, increases minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs and biologic products, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70%, effective January 1, 2019, by the Bipartisan Budget Act of 2018) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Since its enactment, there have been judicial, Congressional and executive challenges to certain aspects of the Affordable Care Act. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the Affordable Care Act brought by several states without specifically ruling on the constitutionality of the Affordable Care Act. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the Affordable Care Act will impact our business.

Prior to the Biden administration, on October 13, 2017, former President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. The former Trump administration concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the Affordable Care Act have not received necessary appropriations from Congress and announced that it will discontinue

these payments immediately until those appropriations are made. Several state Attorneys General filed suit to stop the administration from terminating these subsidies, but on October 25, 2017, a federal judge in California denied their request for a restraining order. On August 14, 2020, the U.S. Court of Appeals for the Federal Circuit ruled in two separate cases that the federal government is liable for the full amount of unpaid cost-sharing reduction, or CSR, payments for the years preceding and including 2017. For CSR claims made by health insurance companies for years 2018 and later, further litigation will be required to determine the amounts due, if any. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in Affordable Care Act risk corridor payments to third-party payors who argued the payments were owed to them. This decision was appealed to the U.S. Supreme Court, which on April 27, 2020, reversed the U.S. Court of Appeals for the Federal Circuit's decision and remanded the case to the U.S. Court of Federal Claims, concluding the government has an obligation to pay these risk corridor payments under the relevant formula. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. While any legislative and regulatory changes will likely take time to develop, and may or may not have an impact on the regulatory regime to which we are subject, we cannot predict the ultimate content, timing or effect of any healthcare reform legislation or the impact of potential legislation on us.

In addition, other legislative and regulatory changes have been proposed and adopted in the United States since the ACA was enacted:

- On April 13, 2017, CMS published a final rule that gives states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

- 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 drug 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 pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

- On May 23, 2019, CMS published a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020.

- On December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repealed the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. At a federal level, President Biden signed an Executive Order on July 9, 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. On September 25, 2020, CMS stated drugs imported by states under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for "best price" or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a

National Average Drug Acquisition Cost for these drugs. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Additionally, on November 30, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. Federal Government will pay for healthcare drugs and services, which could result in reduced demand for our drug candidates or additional pricing pressures.

Individual states in the U.S. have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain drug access and marketing cost disclosure and transparency measures, and designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, financial condition, results of operations and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our drugs or put pressure on our drug pricing, which could negatively affect our business, financial condition, results of operations and prospects.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal drugs for which their national health insurance systems provide reimbursement and to control the prices of medicinal drugs for human use. A member state may approve a specific price for the medicinal drug or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal drug on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical drugs will allow favorable reimbursement and pricing arrangements for any of our drugs. Historically, drugs launched in the European Union do not follow price structures of the U.S. and generally tend to be significantly lower.

Other Healthcare Laws

We may also be subject to healthcare regulation and enforcement by the federal government and the states and foreign governments where we may market our drug candidates, if approved. These laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, privacy and security and physician sunshine laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, any person from knowingly and willfully offering, soliciting, receiving or paying remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs. The government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham consulting and other financial arrangements with physicians. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the

federal False Claims Act. The majority of states also have anti-kickback laws, which establish similar prohibitions and, in some cases, may apply to items or services reimbursed by any third-party payor, including commercial insurers.

In addition, the civil False Claims Act prohibits, among other things, knowingly presenting or causing the presentation of a false, fictitious or fraudulent claim for payment to the U.S. government. Actions under the False Claims Act may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the False Claims Act can result in very significant monetary penalties and treble damages. The federal government is using the False Claims Act, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the U.S., for example, in connection with the promotion of drug for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multi-billion dollar settlements under the False Claims Act in addition to individual criminal convictions under applicable criminal statutes. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

HIPAA also created new federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

We may be subject to federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

There has also been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Affordable Care Act, among other things, imposes new reporting requirements on drug manufacturers for payments made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers are required to submit annual reports to the CMS, which publicly posts the data on its website. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners. Certain states also mandate implementation of compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act and its implementing regulations, collectively referred to as HITECH, and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, we may be subject to state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts.

Additionally, we may be subject to analogous state and foreign laws and regulations, such as state anti-kickback, false claims laws, consumer protection, and unfair competition laws, which may apply to pharmaceutical

business practices, including but not limited to, research, distribution, sales, and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payor, including commercial insurers. Such laws are enforced by various state agencies and through private actions. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant federal government compliance guidance that otherwise restricts payments that may be made to healthcare providers and other potential referral sources, require drug manufacturers to report information related to pricing and marketing information, such as the tracking and reporting of gifts, compensations, and other remuneration and items of value provided to physicians and other healthcare providers and entities, require the registration of pharmaceutical sales representatives, and restrict marketing practices or require disclosure of marketing expenditures. State and foreign laws also govern the privacy and security of health information in certain circumstances. Such data privacy and security laws may differ from one another in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

In the U.S., to help patients afford our approved product, we may utilize programs to assist them, including patient assistance programs and co-pay coupon programs for eligible patients. PAPs are regulated by and subject to guidance from CMS OIG. In addition, at least one insurer has directed its network pharmacies to no longer accept co-pay coupons for certain specialty drugs the insurer identified. Our co-pay coupon programs could become the target of similar insurer actions. In September 2014, the OIG of the HHS issued a Special Advisory Bulletin warning manufacturers that they may be subject to sanctions under the federal anti-kickback statute and/or civil monetary penalty laws if they do not take appropriate steps to exclude Part D beneficiaries from using co-pay coupons. Accordingly, companies exclude these Part D beneficiaries from using co-pay coupons. Further, on December 31, 2020, CMS published a new rule, effective January 1, 2023, requiring manufacturers to ensure the full value of co-pay assistance is passed on to the patient or these dollars will count toward the Average Manufacturer Price and Best Price calculation of the drug. On May 21, 2021, PhRMA sued the HHS in the U.S. District Court for the District of Columbia, to stop the implementation of the rule claiming that the rule contradicts federal law surrounding Medicaid rebates. It is unclear how the outcome of this litigation will affect the rule.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions, and settlements in the healthcare industry. In November 2020, the OIG issued a Fraud Alert highlighting its view that pharmaceutical promotional speaker programs can pose a high risk of fraud and abuse. 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 related governmental regulations that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, individual imprisonment, disgorgement, exclusion of drugs from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, as well as additional oversight, and reporting obligations if we become subject to a corporate integrity agreement or similar settlement to resolve allegations of non-compliance with these laws. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business. Additionally, we may be subject to analogous state and foreign laws and regulations, such as state anti-kickback, false claims laws, consumer protection, and unfair competition laws, which may apply to pharmaceutical business practices, including but not limited to, research, distribution, sales, and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payor, including commercial insurers. Such laws are enforced by various state agencies and through private actions. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant federal government compliance guidance that otherwise restricts payments that may be made to healthcare providers and other potential referral sources, require drug manufacturers to report information related to pricing and marketing information, such as the tracking and reporting of gifts, compensations, and other remuneration and items of value provided to physicians and other healthcare providers and entities, require the registration of pharmaceutical sales representatives, and restrict marketing practices or require disclosure of marketing expenditures. State and foreign laws also govern the privacy and security of health information in certain circumstances. Such data

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Human Capital Resources

We provide an inclusive, collaborative and safe work environment for our employees, who enjoy innovative work and development opportunities. As of January 31, 2022, we had 495 full- and part-time employees globally, approximately 461 of whom are employed in the U.S. and approximately 34 are employed in foreign countries. Of those employees, 278 are engaged in research and development activities and 219 hold Doctorate or Master’s degrees. To allow us flexibility in meeting varying workflow demands, we also engage consultants and temporary workers when needed.

We believe our employees are among the most important assets to our company and are key to achieving our goals and expectations. Accordingly, we focus significant attention on attracting and retaining talented individuals. Our management teams and function leaders regularly review employee engagement and satisfaction surveys and monitor employee turnover rates. To recruit and retain our employees, we offer robust compensation packages, including competitive base pay, incentive compensation and equity programs, and provide a broad range of benefits, including 401(k) plan (pension outside the U.S.), healthcare and insurance benefits, paid time off, paid family and medical leave, flexible work schedules, and various innovative health and wellness programs. In addition, we are committed to the professional development of our employees, who can take advantage of various learning opportunities, such as our mentorship, lunch & learn and skill builder accelerator programs, as well as various training programs.

None of our U.S. employees are represented by a labor union or covered by a collective bargaining agreement. Outside the U.S., our employees in France, Germany and Italy, respectively, are covered by a collective agreement applicable to our industry as required by applicable local law. We consider our relationship with our employees to be good.

Note on the COVID-19 Pandemic

The ongoing COVID-19 pandemic is having widespread, rapidly-evolving, and unpredictable impacts on global societies, economies, financial markets, and business practices. We are closely monitoring the impact of the pandemic, the identification of new variants of the COVID-19 virus and related developments, and our focus remains on promoting employee health and safety when continuing to advance the research and development of our drug candidates and to deliver our approved drugs to patients in need. For discussion regarding the impact of the COVID-19 pandemic on our business and financial results, see "Risk Factors" in Part I, Item 1A and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 of this Annual Report on Form 10-K.

Corporate Information

We were incorporated in the State of Delaware in October 2008 under the name ImmunoCo, Inc. In May 2010, we changed our name to Hoyle Pharmaceuticals, Inc., and in June 2011, we changed our name again to Blueprint Medicines Corporation. Our principal executive offices are located at 45 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 374-7580.

Information Available on the Internet

Our Internet website address is http://www.blueprintmedicines.com. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K. We have included our website address in this in this Annual Report on Form 10-K solely as an inactive textual reference. We make available free of charge through our website our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through the "Investors—SEC Filings" section of our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission, or SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. You can review our electronically filed reports and other information that we file with the SEC on the SEC's website at http://www.sec.gov.

Investors and others should note that we announce material information to our investors using one or more of the following: SEC filings, press releases, public conference calls and webcasts and our corporate website (https://www.blueprintmedicines.com/), including without limitation the "Investors & Media" and "Presentations & Publications" sections of our website. We use these channels, as well as social media channels such as Twitter (@BlueprintMeds) and LinkedIn, to communicate with the public about our company, our business, our approved drugs and drug candidates and other matters. It is possible that the information we post on our corporate website or other social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the "Investors & Media" and "Presentations & Publications" sections of our corporate website and on the social media channels listed on the "Investors & Media" section of our corporate website. The contents of our corporate website and social media channels are not, however, a part of this Annual Report on Form 10-K.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. We believe the risks described below include risks that are material to us as well as other risks that may adversely affect our business, financial condition, results of operations and growth prospects. Please see review the discussion regarding some of the forward-looking statements that are qualified by these risk factors contained elsewhere in this Annual Report on Form 10-K. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Commercialization

We have limited experience as a commercial company and the marketing and sale of AYVAKIT/AYVAKYT, GAVRETO or any future approved drugs may be unsuccessful or less successful than anticipated.

We have two approved precision therapies, AYVAKIT/AYVAKYT and GAVRETO. While we have been commercializing AYVAKIT and GAVRETO in the U.S. and AYVAKYT in Europe, we have limited experience as a commercial company, and there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies commercializing drugs in the biopharmaceutical industry. Marketing applications for avapritinib and pralsetinib are currently under review or planned in the U.S. or globally. To execute our business plan, in addition to successfully marketing and selling our approved drugs, we will need to successfully:

- establish and maintain our relationships with healthcare providers who will be treating patients who may receive our drugs and any future drugs;
- obtain and maintain adequate pricing and reimbursement for AYVAKIT/AYVAKYT, GAVRETO and any future drugs;
- gain regulatory acceptance for the development and commercialization of current or future drug candidates in our pipeline, including for additional indications or in additional geographies for marketed drugs in our portfolio;
- maintain our existing collaborations with Roche and CStone Pharmaceuticals, or CStone;
- expand our global operations or enter into collaboration, partnerships or distribution arrangements in geographies where we may not have current operations or expertise; and
- manage our spending as costs and expenses increase due to clinical trials, marketing approvals, and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to successfully commercialize our current or future approved drugs, develop current or future drug candidates, expand our business or continue our operations.

The commercial success of AYVAKIT/AYVAKYT and GAVRETO, as well as any other drugs that we may bring to the market, will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

AYVAKIT/AYVAKYT and GAVRETO, as well any other drugs that we may bring to the market, may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these drugs do not achieve an adequate level of acceptance, we may not generate significant product revenues and may not become profitable. The degree of market acceptance for AYVAKIT/AYVAKYT and GAVRETO, as well as any current or future drug candidates for which we receive marketing approval, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;

- the prevalence and severity of any side effects, including any limitations or warnings contained in the drug's approved labeling;
- the relative convenience and ease of administration;
- the willingness of eligible patients to try new therapies and of physicians to prescribe these therapies;
- the length of time that patients who are prescribed our drugs remain on treatment;
- the pricing of our drugs and any current or future drug candidates for which we receive marketing approval;
- publicity concerning our current and future drugs, or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

Even if a drug candidate displays a favorable efficacy and safety profile in preclinical and clinical studies and the drug candidate receives marketing approval, market acceptance of the drug will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of our drugs may require significant resources, including more resources than those required for treatments marketed by competitors, and may never be successful. Any of these factors may cause our approved drugs, as well as any current or future drug candidates for which we receive marketing approval, to be unsuccessful or less successful than anticipated.

If we are unable to establish additional commercial capabilities and infrastructure, we may be unable to generate sufficient revenue to sustain our business.

We are continuing to build out our commercial capabilities and infrastructure and have limited sales and distribution experience and limited capabilities for marketing and market access. To successfully commercialize our approved drugs or any current or future drug candidates for which we receive marketing approval, we will need to develop these capabilities and further expand our infrastructure to support commercial operations in the U.S., Europe and other regions, either on our own or with others. We may be competing with many companies that currently have extensive and well-funded marketing and sales operations. Without a significant internal team or the support of a third party to perform these functions, including marketing and sales functions, we may be unable to compete successfully against these more established companies.

We cannot be sure that we will be able to or can successfully compete with other companies to recruit, hire and retain a sufficient number of sales representatives or that they will be effective at promoting our drugs. In addition, we will need to commit significant additional management and other resources to maintain and grow our sales organization. We may not be able to achieve the necessary development and growth in a cost-effective manner or realize a positive return on our investment.

Factors that may inhibit our efforts to commercialize our drugs include:

- our inability to recruit, train and retain adequate numbers of sales and marketing personnel;
- the inability of sales personnel to obtain access to or to persuade adequate numbers of physicians to prescribe our drugs;
- unforeseen costs and expenses associated with maintaining an independent sales and marketing organization; and
- delays or disruptions to sales and marketing activities, including due to the ongoing COVID-19 pandemic.

In the event that we are unable to effectively deploy our sales organization or distribution strategy on a timely and efficient basis, if at all, the commercialization of our drugs could be delayed which would negatively impact our ability to generate product revenues.

If the market opportunities for our approved drugs or drug candidates are smaller than we estimate or if any approval that we obtain is based on a narrower definition of the patient population, our revenue and ability to achieve profitability will be adversely affected.

The precise incidence and/or prevalence for SM, RET-altered cancers, EGFR-mutated NSCLC, CCNE aberrant cancers and GIST are unknown. Our projections of the number of people who have these diseases, the frequency of the genetic alterations targeted by our drugs and drug candidates and the subset of patients who have the potential to benefit from our treatment options are based on estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations or third-party market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these cancers and the number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our approved drugs and drug candidates may be limited or may not be amenable to treatment with our precision therapies.

Accordingly, the number of patients in the U.S., France, Germany, Italy, Spain, the United Kingdom and Japan, which we collectively refer to as the Major Markets, and elsewhere, including the number of addressable patients in those markets, may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our drugs, patients treated with our drugs and drug candidates may develop mutations that confer resistance to treatment or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business.

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

The development and commercialization of new drugs is highly competitive. We face competition with respect to our drugs and current clinical-stage drug candidates, and we will face competition with respect to any drugs and drug candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of therapies in the field of kinase inhibition for cancer and other diseases. Some of these competitive drugs and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Specifically, there are a large number of companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies.

AYVAKIT/AYVAKYT faces competition for advanced SM from Novartis AG's midostaurin and imatinib, and may face competition from drug candidates in development, including that being developed by Cogent Biosciences, Inc. If avapritinib and BLU-263 are approved for non-advanced SM, they may face competition from drug candidates in development, including those being developed by AB Science S.A., Allakos Inc. and Cogent Biosciences, Inc.

GAVRETO faces competition for RET fusion-positive NSCLC and RET-altered thyroid carcinoma, including MTC, from Eli Lilly and Company's selpercatinib. If pralsetinib receives marketing approval for patients with other solid tumors, it will also face competition from selpercatinib for these additional indications. In addition, pralsetinib may face competition from other drug candidates in development for RET-altered cancers, including those being developed by AstraZeneca plc, Boston Pharmaceuticals, Inc., Eisai Inc., Exelixis, Inc., GlaxoSmithKline plc, Mirati Therapeutics, Inc., Novartis AG, Pfizer Inc., Stemline Therapeutics, Inc., and Turning Point Therapeutics, Inc., as well as several approved multi-kinase inhibitors with RET activity being evaluated in clinical trials, including alectinib, apatinib, cabozantinib, dovitinib, lenvatinib, sorafenib, sunitinib and vandetinib.

AYVAKIT/AYVAKYT may face competition from drug candidates in development for PDGFRA-driven GIST, including those being developed by AB Science S.A., ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AROG Pharmaceuticals, Inc., AstraZeneca plc, Celldex Therapeutics, Inc.,

Cogent Biosciences, Inc., Deciphera Pharmaceuticals, LLC, Exelixis, Inc., Ningbo Tai Kang Medical Technology Co. Ltd. and Xencor, Inc.

We are developing BLU-701 and BLU-945 for treatment-resistant EGFR-mutated NSCLC, which, if approved, will face competition from AstraZeneca plc's osimertinib and aumolertinib, which is under collaboration between Jiangsu Hansoh Pharmaceutical Group Co., Ltd. and EQRX, Inc. and approved in China. In addition, BLU-701 and BLU-945 may face competition from drug candidates in development for EGFR-mutated NSCLC, including those being developed by Allist Pharmaceuticals, Arrivent Biopharma, Inc., Betta Pharmaceuticals, Black Diamond Therapeutics, Inc., Boehringer Ingelheim RCV GmbH & Co KG, Bridge Biotherapeutics, Inc., Centessa Pharmaceuticals plc, C4 Therapeutics, Inc., Daiichi Sankyo Company, Limited, Janssen Pharmaceuticals, Inc., Kanaph Therapeutics, Theseus Pharmaceuticals, Inc.

We are developing BLU-451 for EGFR exon 20 insertion-positive NSCLC, which, if approved, will face competition from Janssen Pharmaceuticals, Inc. and Takeda Pharmaceuticals. In addition, BLU-451 may face competition from drug candidates in development for EGFR exon 20 insertion-positive NSCLC, including those being developed by Abbisko Therapeutics Co., Ltd., Bayer AG, Black Diamond Therapeutics, Inc., Centessa Pharmaceuticals plc, Cullinan Oncology, Inc., Daiichi Sankyo Company, Limited, Dizal Pharmaceutical Co. Ltd., Shenzhen Forward Pharmaceutical Co., Ltd., Shanghai Junshi Biosciences Co., Ltd., Oric Pharmaceuticals, Inc., and Scorpion Therapeutics, Inc.

We are developing BLU-222 for cyclin E aberrant cancers, which, if approved, will face competition from indication-specific therapies such as Genentech's bevacizumab, AstraZeneca and Merck's olaparib, Clovis Oncology's rucaparib, GSK's niraparib, Merck's pembrolizumab, and Eisai's lenvatinib. In addition, BLU-222 may face competition from drug candidates in development for cyclin E aberrant cancers, including those being developed by ARC Therapeutics, Inc., Cedilla Therapeutics, Inc., Cyclacel Pharmaceuticals Inc., Monte Rosa Therapeutics, Inc., Nuvation Bio, Inc., Regor Therapeutics Inc., Pfizer Inc., AstraZeneca plc, Zentalis Pharmaceuticals, Inc. and Repare Therapeutics, Inc.

We are developing BLU-852 for advanced cancers susceptible to MAP4K1 inhibition, which, if approved, will face competition from immuno-oncology products, including those developed by Bristol-Myers Squibb Company, Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., Sanofi S.A., and AstraZeneca plc. In addition, BLU-852 may face competition from drug candidates in development for advanced cancers susceptible to MAP4K1 inhibition, including those being developed by Treadwell Therapeutics, Inc., BeiGene Ltd., Nimbus Therapeutics, LLC and MingMed Biotechnology Co., Ltd.

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

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

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any of our approved drugs or drug candidates that we may develop.

We face an inherent risk of product liability exposure related to the testing of our approved drugs and drug candidates in human clinical trials and use of our drug candidates through compassionate use programs, and an even greater risk in connection with our commercialization of our current and future drugs. If we cannot successfully defend ourselves against claims that any of our approved drugs or drug candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any of our approved drugs or drug candidates that we may develop and commercialize;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any of approved drugs or drug candidates that we may develop.

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. We anticipate that we may need to further increase our insurance coverage as we begin additional clinical trials or if we successfully commercialize additional drug candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Increasing demand for compassionate use of our drug candidates could negatively affect our reputation and harm our business.

We are developing drug candidates for the treatment of indications for which there are currently limited or no available therapeutic options. It is possible for individuals or groups to target companies with disruptive social media campaigns related to a request for access to unapproved drugs for patients with significant unmet medical need. If we experience a similar social media campaign regarding our decision to provide or not provide access to any of our current or future drug candidates under an expanded access policy, our reputation may be negatively affected and our business may be harmed.

Recent media attention to individual patients' expanded access requests has resulted in the introduction and enactment of legislation at the local and national level referred to as "Right to Try" laws, such as the federal Right to Try Act of 2017, which are intended to allow patients access to unapproved therapies earlier than traditional expanded access programs. A possible consequence of both activism and legislation in this area may be the need for us to initiate an unanticipated expanded access program or to make our drug candidates more widely available sooner than anticipated.

In addition, some patients who receive access to drugs prior to their commercial approval through compassionate use, expanded access programs or right to try access, collectively referred to as compassionate use programs, have life-threatening illnesses and have exhausted all other available therapies. The risk for serious adverse events in this patient population is high, which, if those adverse events are determined to be drug-related, could have a negative impact on the safety profile of our drug candidates if we were to provide them to these patients, which could cause significant delays or an inability to successfully commercialize our drug candidates and materially harm our business. If we were to provide patients with any of our drug candidates under a compassionate use program, our supply capabilities may limit the number of patients who are able to enroll in the program and we may in the future need to restructure or pause any compassionate use program in order to enroll sufficient numbers of patients in our controlled

clinical trials required for regulatory approval and successful commercialization of our drug candidates, which could prompt adverse publicity or other disruptions related to current or potential participants in such programs.

If we or our collaborators are unable to successfully develop and commercialize companion diagnostic tests for our drugs and drug candidates, or experience significant delays in doing so we may not realize the full commercial potential of our drugs and drug candidates.

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our drugs and drug candidates, we believe that our success may depend, in part, on the development and commercialization of companion diagnostic tests. There has been limited success to date industrywide in developing and commercializing these types of companion diagnostic tests. To be successful, we need to address a number of scientific, technical and logistical challenges. We have entered into agreements to develop and/or commercialize companion diagnostic tests with third parties, including for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, and pralsetinib in order to identify NSCLC patients with RET fusions and MTC patients with RET mutations. We have limited experience in the development and commercialization of companion diagnostic tests with third parties and may not be successful in developing and commercializing appropriate companion diagnostic tests with third parties to pair with our approved drugs or drug candidates that receive marketing approval. In addition, current commercially available diagnostic tests may become unavailable in the future. Companion diagnostic tests are subject to regulation by the FDA and similar regulatory authorities outside the U.S. as medical devices and require separate regulatory clearance or approval prior to commercialization. We are relying on third parties to design, manufacture, obtain regulatory clearance or approval for and commercialize the companion diagnostic tests, including for avapritinib and pralsetinib, and we expect to rely in whole or in part on third parties to design, manufacture, obtain regulatory clearance or approval for and commercialize any other companion diagnostic tests for current and future drug candidates. We and our collaborators may encounter difficulties in developing and obtaining clearance or approval for the companion diagnostic tests, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. In addition, our collaborators for any companion diagnostic test that we may seek to develop:

- may not perform their respective obligations as expected or as required under our agreements with them;
- may not pursue commercialization of a companion diagnostic test even if it receives any required regulatory clearances or approvals;
- may elect not to continue the development of a companion diagnostic test based on changes in their or other third parties' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- may not commit sufficient resources to the marketing and distribution of a companion diagnostic test; and
- may terminate their relationship with us.

Any delay or failure by us or our collaborators to develop or obtain regulatory clearance or approval of the companion diagnostic tests could delay, prevent or revoke approval of our drug candidates. If we, or any third parties that we have engaged or may in the future engage to assist us are unable to successfully develop and commercialize companion diagnostic tests for our drugs and drug candidates, or experience delays in doing so:

- the development of our approved drugs and drug candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our drug candidates may not receive marketing approval if safe and effective use of a therapeutic drug candidate depends on an in vitro diagnostic;
- regulatory authorities may impose post-marketing requirements regarding the development and commercialization of companion diagnostic tests for our drugs and drug candidates; and

- we may not realize the full commercial potential of any of our approved drugs or drug candidates that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from treatment with our drugs.

As a result, our business may be materially harmed.

In addition, third party collaborators may encounter production difficulties that could constrain the supply of the companion diagnostic tests, and both they and we may have difficulties gaining acceptance of the use of the companion diagnostic tests in the clinical community. If such companion diagnostic tests fail to gain market acceptance, it would have an adverse effect on our ability to derive revenues from sales of our current and future drugs. In addition, the 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 our approved drugs and drug 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 drugs and drug candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our drugs and drug candidates.

Our reliance on single-source third-party suppliers could harm our ability to commercialize our drugs or any drug candidates that may be approved in the future.

We do not currently own or operate manufacturing facilities for the production of our drugs or any drug candidates that may be approved in the future. We primarily rely on single-source third-party suppliers to manufacture and supply our drugs, which may not be able to produce sufficient inventory to meet commercial demand in a timely manner, or at all. Our third-party suppliers may not be required to provide us with any guaranteed minimum production levels or have dedicated capacity for our drugs. As a result, there can be no assurances that we will be able to obtain sufficient quantities of our drugs or any other drug candidates that may be approved in the future, which could have a material adverse effect on our business as a whole.

If, in the future, we are unable to maintain sales and marketing capabilities or enter into agreements with third parties to sell and market our drugs and drug candidates, we may not be successful in commercializing our drugs and drug candidates if and when they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time-consuming and could delay any drug launch. If the commercial launch of a drug candidate for which we establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses, which may be costly.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our drug revenues or the profitability of these drug revenues to us are likely to be lower than if we were to market and sell any current or future drugs ourselves. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our drugs effectively. In addition, we may not be successful in entering into arrangements with third parties to sell and market our current and future drugs or may be unable to do so on terms that are favorable to us.

If we do not establish and maintain sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our drugs and drug candidates, if approved. Further, our business, results of operations, financial condition and prospects will be materially adversely affected.

Risks Related to Drug Development and Regulatory Approval

If we are unable to advance our drug candidates to clinical development, obtain regulatory approval for our drug candidates, including for avapritinib and pralsetinib in additional indications or in additional geographies, and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed.

Our ability to generate substantial drug revenues, if ever, will depend heavily on the successful development and commercialization of our drugs and drug candidates. Each of our drug candidates will require additional preclinical or clinical development, management of clinical, preclinical and manufacturing activities, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, substantial investment and significant marketing efforts before we generate substantial revenues from sales for those drug candidates, if approved. In addition, for some of our drug candidates, in order to select patients most likely to respond to treatment and rapidly confirm mechanistic and clinical proof-of-concept, or to identify appropriate patients for our drugs or drug candidates for which we obtain approval, we may be required or we may seek to develop companion diagnostic tests, which are assays or tests to identify an appropriate patient population. Companion diagnostic tests are subject to regulation as medical devices and must themselves be cleared or approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our drug candidates. The success of our approved drugs and drug candidates will depend on several factors, including the following:

- successful enrollment in, and initiation and completion of, clinical trials, including our ongoing and planned clinical trials for our drugs and drug candidates;
- successful initiation and completion of preclinical studies for our other drug candidates;
- successful development of any companion diagnostic tests for use with our drugs and drug candidates;
- receipt of regulatory approvals from applicable regulatory authorities and transitioning any conditional marketing authorizations to full approvals;
- in-house commercial manufacturing capabilities or arrangements with third-parties for clinical supply and commercial manufacturing, packaging and labeling and the receipt by such third-party manufacturers of requisite approvals to supply commercial inventories of our approved drugs and drug candidates;
- obtaining and maintaining patent and trade secret protection or regulatory exclusivity for our drugs and drug candidates;
- successful commercialization of our approved drugs and drug candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of our approved drugs and drug candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- enforcing and defending intellectual property rights and claims; and
- maintaining a continued acceptable safety profile of our drugs and drug candidates following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our drugs and drug candidates, which would materially harm our business. If we do not receive regulatory approvals for our drug candidates, we may not be able to continue our operations.

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

We may not be able to initiate or continue clinical trials for our drug candidates, including avapritinib and pralsetinib for additional indications, if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the U.S. Because the target patient populations for our drug candidates and approved drugs in clinical development for additional indications are relatively small, it may be difficult to successfully identify patients. Although we have entered into or plan to enter into agreements with third parties to develop companion diagnostic tests for use in some of our other current or future clinical trials in order to help identify eligible patients, we may experience delays in reaching, or fail to reach, agreement on acceptable terms to develop such companion diagnostic tests. Any third parties whom we engage to develop companion diagnostic tests may experience delays or may not be successful in developing such companion diagnostic tests, furthering the difficulty in identifying patients for our clinical trials. In addition, current commercially available diagnostic tests to identify appropriate patients for our clinical trials or any approved drug candidates may become unavailable in the future.

In addition, we have experienced some delays or disruptions in enrollment in our ongoing clinical trials due to the COVID-19 pandemic, and we anticipate we may experience additional delays or disruptions in the future due to the ongoing COVID-19 pandemic and changes in local site or IRB policies availabilities of site staff reprioritization of hospital resources, restricted access to healthcare professionals and testing sites and other containment measures or concerns among patients about participating in clinical trials during a pandemic. Furthermore, some of our competitors have ongoing clinical trials for drug candidates that treat the same indications as our drug candidates and approved drugs in clinical development for additional indications, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' drug candidates.

Patient enrollment may be affected by other factors including:

- the severity of the disease under investigation;
- the size of the target patient population;
- the eligibility criteria for the clinical trial;
- the availability of an appropriate genomic screening test;
- the perceived risks and benefits of the drug candidate under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to identify patients appropriate for enrollment in our clinical trials, or to enroll a sufficient number of patients in our clinical trials, would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our drug candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. If we are unable to include patients with the driver of the disease, including the applicable genomic alteration for diseases in genomically defined patient populations, this could compromise our ability to seek participation in the FDA's expedited review and approval programs, including breakthrough therapy designation and fast track designation, or otherwise to seek to accelerate clinical development and regulatory timelines.

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals for our drug candidates and, if applicable, for any related companion diagnostic tests, we will not be able to commercialize, or may be delayed in commercializing, such drug candidates, and our ability to generate revenue will be materially impaired.

Our drug candidates and any companion diagnostic tests related to our approved drugs or drug candidates, including the companion diagnostic tests that we are developing or have developed for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, and pralsetinib in order to identify NSCLC patients with RET fusions and MTC patients with RET mutations, and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, distribution, import and export, are subject to comprehensive regulation by the FDA and other regulatory agencies in the U.S. and by comparable authorities in other countries. Before we can commercialize any of our drug candidates, we must obtain marketing approval. We may also need marketing clearance or approval for any related companion diagnostic tests, including the companion diagnostic tests that we are developing for avapritinib and pralsetinib.

We expect to rely on third-party CROs and/or regulatory consultants to assist us in filing and supporting the applications necessary to gain regulatory approvals. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the drug candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the drug manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Should FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel, FDA has stated that it generally intends to issue a complete response letter. Further, if there is inadequate information to make a determination on the acceptability of a facility, FDA may defer action on the application until an inspection can be completed. Our drug candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining regulatory approvals, if approval is obtained at all, both in the U.S. and abroad is expensive, may take many years if additional clinical trials are required and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the drug candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted NDA for a drug candidate, pre-market approval, or PMA, application for a companion diagnostic test or equivalent application types, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. We currently have multiple marketing applications for our drug candidates under review across the world.

Our drug candidates could be delayed in receiving, or fail to receive, regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a drug candidate is safe and effective for its proposed indication or a related companion diagnostic test is suitable to identify appropriate patient populations;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that a drug candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;

- the data collected from clinical trials of our drug candidates may not be sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the U.S. or elsewhere;

- the FDA or comparable foreign regulatory authorities may find deficiencies with or fail to approve the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies;

- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval; and

- delays or disruptions impacting the FDA or comparable foreign regulatory authorities due to the ongoing COVID-19 pandemic.

As of May 26, 2021, the FDA noted it is 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. On July 16, 2020, FDA noted that it is continuing to expedite oncology product development with its staff teleworking full-time. However, 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 ongoing COVID-19 pandemic and travel restrictions FDA is unable to complete such required inspections during the review period. In 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. In addition, even if we were to obtain approval, regulatory authorities may approve any of our drug candidates for fewer or more limited indications than we request, may not approve the price we intend to charge for our drugs and related companion diagnostic tests, may grant approval contingent on the performance of costly post-marketing clinical trials or other post-marketing requirements, or may approve a drug candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that drug candidate. Any of the foregoing scenarios could materially harm the commercial prospects for our drug candidates.

If we experience delays in obtaining approval or if we fail to obtain approval of our drug candidates and companion diagnostic tests related to our approved drugs and drug candidates, the commercial prospects for our approved drugs or drug candidates may be harmed and our ability to generate revenues will be materially impaired.

Results from earlier stage trials may not be predictive of the results of later stage trials and interim and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available or as additional analyses are conducted and as the data are subject to audit and verification procedures that could result in material changes in the final data.

The results of preclinical studies and early clinical trials of our drug candidates may not be predictive of the results of later-stage clinical trials. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. There is typically an extremely high rate of attrition from the failure of drug candidates proceeding through clinical trials. Drug 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. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or emergence of unacceptable safety issues, notwithstanding promising results in earlier trials. Most drug candidates that commence clinical trials are never approved as products and there can be no assurance that any of our future clinical trials will ultimately be successful or support further clinical development of any of our drug candidates. Drug candidates that appear promising in the early phases of development may fail to reach the market for several reasons, including:

- preclinical studies or clinical trials may show the drug candidates to be less effective than expected (e.g., a clinical trial could fail to meet its primary endpoint(s)) or to have unacceptable side effects or toxicities;

- failure to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful;

- failure to receive the necessary regulatory approvals;

- manufacturing issues, formulation issues, pricing or reimbursement issues or other factors that make a drug candidate uneconomical; and

- the proprietary rights of others and their competing products and technologies that may prevent one of our drug candidates from being commercialized.

In addition, differences in trial design between early-stage clinical trials and later-stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials. Moreover, clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their drug candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their products.

Additionally, from time to time, we may publish interim or preliminary data from our clinical studies. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary 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, interim and preliminary data should be viewed with caution until the final data are available. Material adverse changes between preliminary or interim data and final data could significantly harm our business prospects.

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

Undesirable side effects caused by any of our approved drugs or drug candidates could cause us to interrupt, delay or halt preclinical studies or could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other regulatory authorities. As is the case with all oncology drugs, it is likely that there may be side effects associated with the use of our drugs and drug candidates. Results of our trials could reveal a high and unacceptable severity and prevalence of these or other side effects. In such an event, our trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of our drugs or drug candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete clinical trials or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, our approved drugs and drug candidates could cause undesirable side effects in preclinical studies or clinical trials related to on-target toxicity. If on-target toxicity is observed, or if our drugs or drug candidates have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in early stage testing for treating cancer have later been found to cause side effects that prevented further development of the compound.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our drugs or drug candidates may only be uncovered with a significantly larger number of patients exposed to the drugs or drug candidate. If we or others identify undesirable side effects caused by any of our approved drugs or drug candidates (or any other similar drugs) after marketing approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such drug;

- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;

- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;

- we may be required to change the way such drug is distributed or administered, conduct additional clinical trials or change the labeling of such drug;

- regulatory authorities may require a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;

- we may be subject to regulatory investigations and government enforcement actions;

- we may decide to remove such drug from the marketplace;

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

- our reputation may suffer.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected drugs or drug candidates and could substantially increase the costs of commercializing our approved drugs and drug candidates, if approved, and significantly impact our ability to successfully commercialize our approved drugs and drug candidates and generate revenues.

A breakthrough therapy designation by the FDA for our drug candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our drug candidates will receive marketing approval.

We may seek breakthrough therapy designation for some of our current or future drug candidates. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. The FDA has granted breakthrough therapy designation to avapritinib for the treatment of moderate to severe indolent SM. In addition, the FDA previously granted breakthrough designation to our drugs, AYVAKIT and GAVRETO, for the treatment of certain patients with GIST, advanced SM and RET-altered cancers, respectively.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our drug candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a drug candidate may not result in a faster development process, review or approval compared to other drugs and does not assure ultimate approval by the FDA. In addition, even if one or more of our drug candidates qualify as breakthrough therapies, the FDA may later decide that the drugs no longer meet the conditions for qualification. On May 26. 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; however, the FDA may not be able to continue its current pace and review timelines could be extended, including due to the inability for the FDA to complete any inspections of manufacturing facilities or clinical sites that may be required for an approval.

We may be unsuccessful in obtaining or may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

The FDA has granted orphan drug designation to avapritinib for the treatment of GIST and the treatment of mastocytosis, to pralsetinib for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC and to fisogatinib for the treatment of HCC. In addition, the European Commission has granted medicinal product designation to avapritinib for the treatment of GIST and the treatment of mastocytosis. As part of our business strategy, we may seek orphan drug designation for some of our other drug candidates, and we may be unsuccessful. Regulatory authorities in some jurisdictions, including the U.S. and the European Union, may designate drugs for

relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is 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 developing the drug will be recovered from sales in the U.S. 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.

Similarly, in the EU, the European Commission grants orphan medicinal product designation after receiving the opinion of the European Medicines Agency, or EMA, Committee for Orphan Medicinal Products on an orphan medicinal product designation application. Orphan medicinal product designation is intended to promote the development of drugs that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five (5) in ten thousand (10,000) persons in the EU and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the drug would be a significant benefit to those affected). In addition, designation is granted for drugs intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the drug. In the EU, orphan medicinal product designation entitles a party to financial incentives such as reduction of fees or fee waivers.

Generally, if a drug with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same drug and indication for that time period, except in limited circumstances. The applicable period is seven years in the U.S. and ten years in the EU. The EU 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 exclusivity for a drug, that exclusivity may not effectively protect the designated drug from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug 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.

On August 3, 2017, Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's preexisting regulatory interpretation, to require that a drug Sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The law reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. Moreover, in the Consolidated Appropriations Act of 2021, Congress did not further change this interpretation when it clarified that the interpretation codified in FDARA would apply in cases where FDA issued an orphan designation before the enactment of FDARA but where product approval came after the enactment of FDARA. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. 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. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Moreover, orphan drug exclusive marketing rights in the U.S. may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. While we intend to continue seek orphan drug designation for our drug candidates, we may never receive such designations. Even if we receive orphan drug designation for any of our drug candidates, there is no guarantee that we will enjoy the benefits of those designations.

The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. 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.

We may not be successful in our efforts to expand our pipeline of drug candidates.

A key element of our strategy is to use our novel target discovery engine to identify kinases that are drivers of diseases in genomically defined patient populations with high unmet medical need in order to build a pipeline of drug candidates. Although our research and development efforts to date have resulted in a pipeline of drug candidates, we may not be able to continue to identify novel kinase drivers and develop drug candidates. We may also pursue opportunities to acquire or in-license additional businesses, technologies or drugs, form strategic alliances or create joint ventures with third parties to complement or augment our existing business. However, we may not be able to identify any drug candidates for our pipeline through such acquisition or in-license.

Even if we are successful in continuing to build and expand our pipeline, the potential drug candidates that we identify may not be suitable for clinical development. For example, they may be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will be successful in clinical trials or receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize drug candidates, we will not be able to obtain drug revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

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

Because we have limited human capital and financial resources, we focus on research programs and drug candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other drug candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and drug candidates for specific indications may not yield any commercially viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such drug candidate.

At any time and for any reason, we may determine that one or more of our discovery programs or preclinical or clinical drug candidates or programs does not have sufficient potential to warrant the allocation of resources toward such program or drug candidate. Accordingly, we may choose not to develop a potential drug candidate or elect to suspend, deprioritize or terminate one or more of our discovery programs or preclinical or clinical drug candidates or programs. If we suspend, deprioritize or terminate a program or drug candidate in which we have invested significant resources, we will have expended resources on a program that will not provide a full return on our investment and may have missed the opportunity to have allocated those resources to potentially more productive uses, including existing or future programs or drug candidates.

Risks Related to Government Legislations and Regulations

We are required to comply with comprehensive and ongoing regulatory requirements for any of our current or future approved drugs, including conducting confirmatory clinical trials for any drug that receives accelerated approval. In addition, our current or future approved drugs could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drugs.

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

If the FDA or a comparable foreign regulatory authority approves any of our drug candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and

recordkeeping for the drug 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 continued compliance with current Good Manufacturing Practices, or cGMPs, and Good Clinical Practices, or GCPs, for any clinical trials that we conduct post-approval. Any regulatory approvals that we receive for our drug candidates may also be subject to limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the drug. Later discovery of previously unknown problems with a drug, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the drug, withdrawal of the drug from the market, "dear doctor" letters or drug recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of marketing approvals;
- drug seizure or detention, or refusal to permit the import or export of drugs; and
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our drug candidates. 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, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

Regulatory agencies may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, or DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use, and if we, or any future collaborators, do not market any of our products for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing, government investigations, or litigation. Violation of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state healthcare fraud and abuse laws and state consumer protection laws.

Even if we are able to commercialize any of our approved drugs or drug candidates, if approved, such drug or drug candidate may become subject to unfavorable pricing regulations or third-party coverage and reimbursement policies, which would harm our business.

The regulations that govern regulatory approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a drug candidate in a particular country, but then be subject to price regulations that delay our commercial launch of the drug candidate, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the drug candidate in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more drug candidates, even if our drug candidates obtain marketing approval.

Our ability to commercialize any drugs and drug candidates successfully also will depend in part on the extent to which coverage and reimbursement for these drugs and drug candidates and related treatments will be available from government authorities, private health insurers and other organizations. In the U.S. and markets in other countries,

patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance. Our ability to successfully commercialize additional products will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree. The availability of coverage and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford treatments. Sales of these or other products that we may identify will depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If coverage and adequate reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our products. 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 a sufficient return on our investment. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular drugs. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for drugs. We cannot be sure that coverage will be available for any drug candidate that we commercialize and, if coverage is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any drug candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any drug candidate for which we obtain marketing approval. Further, due to the ongoing COVID-19 pandemic, many individuals have lost or will be losing employer-based insurance coverage, which may adversely affect our ability to commercialize our products. It is unclear what effect, if any, American Rescue Plan and other government efforts to expand coverage will have on the number of covered individuals. See section entitled "*Business – Coverage and Reimbursement*."

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or similar regulatory authorities outside the U.S. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower-cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Private third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved drugs that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize drugs and our overall financial condition.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

The United States has enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our current drug candidates or any future drug candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business. In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. For example, in March 2010, the ACA was passed, which substantially changes the way healthcare is financed by both governmental and private

insurers, and significantly impacts the U.S. pharmaceutical industry. See section entitled "*Business – Coverage and Reimbursement*."

At the state level, legislatures have increasingly passed legislation and implemented 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.

We may face competition in the U.S. for our development candidates and investigational medicines, if approved, from therapies sourced from foreign countries that have placed price controls on pharmaceutical products. Proponents of drug reimportation may attempt to pass legislation that would directly allow reimportation under certain circumstances. Legislation or regulations allowing the reimportation of drugs, if enacted, could decrease the price we receive for any products that we may develop and adversely affect our future revenues and prospects for profitability.

The Creating and Restoring Equal Access to Equivalent Samples Act, or the CREATES Act, was enacted in 2019 requiring sponsors of approved new drug applications and biologics license applications to provide sufficient quantities of product samples on commercially reasonable, market-based terms to entities developing generic drugs and biosimilar biological products. The law establishes a private right of action allowing developers to sue application holders that refuse to sell them product samples needed to support their applications. If we are required to provide product samples or allocate additional resources to responding to such requests or any legal challenges under this law, our business could be adversely impacted.

Other legislative measures have also been enacted that may impose additional pricing and product development pressures on our business, and we expect that additional foreign, federal and state 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 limited coverage and reimbursement and reduced demand for our drugs and drug candidates, if approved, or additional pricing pressures.

We are currently unable to predict what additional legislation or regulation, if any, relating to the health care industry may be enacted in the future or what effect recently enacted federal legislation or any such additional legislation or regulation would have on our business. The pendency or approval of such proposals or reforms could result in a decrease in our stock price or limit our ability to raise capital or to enter into collaboration agreements for the further development and commercialization of our approved drugs and drug candidates.

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

Our arrangements with third-party payors and customers expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including but not limited to, the federal healthcare Anti-Kickback Statute, the False Claims Act, the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, the Physician Payment Sunshine Act, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, the federal false statements statute, federal consumer protection and unfair competition laws and similar state and foreign laws and regulations that may regulate the business or financial arrangements and relationships through which we market, sell and distribute our drugs. The number and complexity of federal, state, and foreign laws continue to increase, and additional governmental resources are being used to enforce these laws and to prosecute companies and individuals who are believed to be violating them. See section entitled "*Business – Other Healthcare Laws*."

In the U.S., to help patients who have no or inadequate insurance access our drug, we have a patient assistance program that we administer in conjunction with our patient support program vendor. If we or our vendors are deemed to fail to comply with relevant laws, regulations or evolving government guidance in the operation of these programs, we could be subject to damages, fines, penalties or other criminal, civil or administrative sanctions or enforcement actions. We cannot ensure that our compliance controls, policies and procedures will be sufficient to protect against acts of our employees, business partners or vendors that may violate the laws or regulations of the jurisdictions in which we operate. Regardless of whether we have complied with the law, a government investigation could impact our business practices,

harm our reputation, divert the attention of management, increase our expenses and reduce the availability of assistance to our patients.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could involve substantial costs. It is possible that governmental authorities will conclude that our business practices do 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, including anticipated activities to be conducted by our sales team, were to be found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs.

Our future growth may depend, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability may depend, in part, on our ability to commercialize current or future drug candidates in foreign markets for which we may rely on collaboration with third parties. We are not permitted to market or promote any of our drug candidates before we receive regulatory approval from the applicable regulatory authority in that foreign market. To obtain separate regulatory approval in many other countries we must comply with numerous and varying regulatory requirements of such countries regarding safety and efficacy and governing, among other things, clinical trials, manufacturing, commercial sales, pricing and distribution of our drug candidates, and we cannot predict success in these jurisdictions. If we seek to develop our drug candidates or obtain approval of our drug candidates and ultimately commercialize our drug candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for our drug candidates in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, including the European General Data Protection Regulation 2016/679, commonly referred to as GDPR;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- the existence of additional potentially relevant third-party intellectual property rights;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of our drug candidates could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

Governments outside the U.S. tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, particularly countries in the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. 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 drug candidate to other available therapies. If reimbursement of our drugs is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

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

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

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

Risks Related to Our Financial Position and Need for Additional Capital

We are a precision therapy company with a limited operating history. We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.

We are a precision therapy company with a limited operating history. To date, we have not yet demonstrated our ability to conduct large-scale sales and marketing activities necessary for successful commercialization. We currently have two approved precision therapies and are transitioning to a company capable of supporting commercial activities. We may not be successful in such a transition.

We commenced operations in April 2011 and we have focused substantially all of our efforts and financial resources to date on organizing and staffing our company, business planning, raising capital, establishing our intellectual property building our discovery platform, including our proprietary compound library and new target discovery engine, identifying kinase drug targets and potential drug candidates, conducting preclinical studies and clinical development for our drug candidates, commencing pre-commercial activities and the commercial launches for AYVAKIT/AYVAKYT and GAVRETO, and producing the active pharmaceutical ingredient, or API, drug substance and drug product material for use in preclinical studies and clinical trials for our drug candidates and commercial sale of our approved drugs.

To date, we have financed our operations primarily through public offerings of our common stock, private placements of our convertible preferred and common stock, collaborations and a license agreement. Through December 31, 2021, we have received an aggregate of $3.0 billion from such transactions, including $1.9 billion in aggregate gross proceeds from the sale of common stock in our initial public offering, follow on public offerings, through our "at the market" stock offering program and the equity investment by Roche, $115.1 million in gross proceeds from the issuance of convertible preferred stock, $996.3 million in upfront payments and milestone payments under our collaborations with Roche, CStone and Zai, our license agreement with Clementia and our former collaboration with Alexion. In addition, since January 2020, we also have generated revenue through sales of our drug products.

Since inception, we have incurred significant operating losses, with the exception of the year ended December 31, 2020. Our net loss was $644.1 million for the year ended December 31, 2021. Our net income was $313.9 million for the year ended December 31, 2020 primarily due to the collaboration revenue recorded under our collaboration with

Roche for pralsetinib, and our net loss was $347.7 million for the year ended December 31, 2019. As of December 31, 2021, we had an accumulated deficit of $1,275.4 million.

Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant expenses and operating losses over the next few years. We anticipate that our expenses will continue to increase in connection with our ongoing activities. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses to significantly increase in connection with continuing our existing clinical trials and beginning additional clinical trials. In addition, we will incur significant sales, marketing and outsourced-manufacturing expenses in connection with the commercialization of any of our drugs or any drug candidates for which we may receive marketing approval. In addition, we have incurred and will continue to incur substantial costs associated with operating as a public company. Because of the numerous risks and uncertainties associated with developing pharmaceuticals, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis. Our ability to become profitable depends upon our ability to generate substantial revenue.

To date, we have not generated substantial revenue from drug sales. Our ability to generate substantial revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete clinical trials that meet their clinical endpoints;
- initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approval for our drug candidates, including for avapritinib and pralsetinib for additional indications or in additional geographies;
- continue to maintain and expand commercial manufacturing capabilities or make arrangements with third-party manufacturers for clinical supply and commercial manufacturing;
- maintain and, if necessary, expand a sales, marketing and distribution infrastructure to commercialize AYVAKIT/AYVAKYT, GAVRETO and any current or future drug candidates for which we obtain marketing approval; and
- achieve market acceptance in the medical community and with third-party payors for AYVAKIT/AYVAKYT, GAVRETO and any current or future drug candidates for which we receive marketing approval.

We expect to incur significant sales and marketing costs as we commercialize AYVAKIT/AYVAKYT, jointly commercialize GAVRETO with Roche and commercialize any current or future drug candidates for which we receive marketing approval. Even if we initiate and successfully complete pivotal clinical trials of our drug candidates, and our drug candidates are approved for commercial sale, and despite expending these costs, our drug candidates may not be commercially successful. We may not achieve profitability soon after generating drug sales, if ever. If we are unable to generate substantial drug revenue, we will not become profitable and may be unable to continue operations without continued funding.

We may seek to raise additional funding from time to time. If we are unable to raise capital when needed, we may be forced to delay, reduce or eliminate some of our drug development programs or commercialization efforts.

The development and commercialization of pharmaceuticals is capital-intensive. We are currently advancing multiple drug candidates and development programs through clinical and preclinical development. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate or continue clinical trials of, and seek marketing approval for our drug candidates, including marketing approval for avapritinib for additional indications or in additional geographies and for pralsetinib. In addition, we expect to incur additional significant commercialization expenses for AYVAKIT/AYVAKYT, GAVRETO and other drug candidates, if approved, related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of potential collaborators or licensors. We may also

need to raise additional funds if we choose to pursue additional indications or geographies for any of our approved drugs or drug candidates or otherwise expand more rapidly than we presently anticipate.

Our future capital requirements will depend on and could increase significantly as a result of many factors, including:

- the success of our commercialization efforts and market acceptance for AYVAKIT/AYVAKYT, GAVRETO or any of our current or future drug candidates for which we receive marketing approval;
- the costs of maintaining, expanding or contracting for sales, marketing and distribution capabilities in connection with commercialization of AYVAKIT/AYVAKYT, GAVRETO and any of our current or future drug candidates for which we receive marketing approval;
- the costs of securing manufacturing, packaging and labeling arrangements for development activities and commercial production, including API, drug substance and drug product material for use in preclinical studies, clinical trials, our compassionate use program and for use as commercial supply , as applicable;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our approved drugs and drug candidates;
- the costs, timing and outcome of regulatory review of marketing applications for our drug candidates, including seeking marketing approval for avapritinib and pralsetinib for additional indications or in additional geographies;
- the success of our collaborations with Roche, CStone and Zai Lab and our license agreement with Clementia, as well as our ability to establish and maintain additional collaborations, partnerships or licenses on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under our existing collaboration or license agreements, or any collaboration, partnership or license agreements that we may enter into in the future;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, research and development, clinical or other costs under future collaboration agreements, if any;
- the extent to which we acquire or in-license other approved drugs, drug candidates or technologies and the terms of any such arrangements;
- the success of our current or future collaborations for the development and commercialization of companion diagnostic tests;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- the costs of continuing to expand our operations.

Accordingly, we may seek additional funding in connection with our continuing operations or business objectives. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize any of our approved drugs or drug candidates. We cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. We could also be required to seek funds through collaborations, partnerships, licensing arrangements or otherwise at an earlier stage than would be desirable and we may be required to relinquish rights to some of our

technologies, drugs or drug candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis or on attractive terms, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any of our approved drugs or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

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

Until such time, if ever, as we can generate substantial drug revenues, we expect to finance our cash needs primarily through a combination of public and private equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations with Roche, CStone and Zai Lab and the license agreement with Clementia, which are limited in scope and duration and subject to the achievement of milestones or royalties on sales of licensed products, if any. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that materially adversely affect the rights of our common stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Risks Related to Our Dependence on Third Parties

We have entered into collaborations and licenses with our partners for the development and commercialization of several of our drugs and drug candidates. If our collaborations are not successful, we may not be able to capitalize on the market potential of these drugs and drug candidates.

We have entered into collaborations and licenses with Roche, CStone, Zai Lab and Clementia, for the development and commercialization of several of our drugs and drug candidates, and may enter into additional collaborations and licenses with other third parties in the future. The success of these arrangements will depend heavily on the efforts and activities of our collaborators and licensing partners. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. In some situations, we may not be able to influence our collaboration partners' decisions regarding the development and collaboration of our partnered drugs and drug candidates, and as a result, our collaboration partners may not pursue or prioritize the development and commercialization of those partnered drugs and drug candidates in a manner that is in our best interest. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable drug candidate and, in some cases, termination of the collaboration arrangement or result in litigation or arbitration, which would be time-consuming and expensive. Licensors generally have sole discretion in determining the efforts and resources that they will apply to the licensed products.

Collaborations and licenses with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. For example, in the fourth quarter of 2017, Alexion terminated our collaboration related to fibrodysplasia ossificans progressiva for convenience following a strategic review by Alexion of its research and development portfolio. Any termination or expiration of our collaboration or license agreements with Roche, CStone, Zai Lab or Clementia, or of any future collaboration or license agreement, could adversely affect us financially or harm our business reputation.

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

We do not have the ability to independently conduct clinical trials. We rely on medical institutions, clinical investigators, CROs, contract laboratories and other third parties to conduct or otherwise support clinical trials for our approved drugs and drug candidates. We rely heavily on these parties for execution of clinical trials for our drugs and drug candidates and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on CROs will not relieve us of our regulatory responsibilities. For any violations of laws and regulations during the conduct of our clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

We and our CROs are required to comply with regulations, including GCPs, for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any drugs in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that our current or future clinical trials comply with GCPs. In addition, our clinical trials must be conducted with drug candidates produced under cGMPs regulations. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Although we intend to design and sponsor the clinical trials for our approved drugs and drug candidates, CROs will conduct all of our clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct current or future clinical trials will also result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

Some of these factors may be beyond our control. For example, the performance of our CROs may also be delayed or disrupted by the ongoing COVID-19 pandemic, including due to travel or quarantine policies, availabilities of staff, exposure of CRO staff to COVID-19 or re-prioritization of CRO resources as a result of the pandemic. These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If the CROs do not perform clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development, regulatory approval and commercialization of our approved drugs for additional indications and our drug candidates may be delayed, we may not be able to obtain regulatory approval and commercialize our drug candidates, or our development program materially and irreversibly harmed. If we are unable to rely on clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of any clinical trials we conduct and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical trials such CROs are associated with may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our drug for additional indications or our drug candidates. As a result, we believe that our financial results and the commercial prospects for our drugs or our drug candidates in the subject indication would be harmed, our costs could increase and our ability to generate substantial revenue could be delayed.

We contract with third parties for the manufacture of our approved drugs and drug candidates, including for preclinical, clinical and commercial supply. This reliance on third parties increases the risk that we will not have sufficient quantities of our approved drugs or drug candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not currently own or operate, nor do we have any plans to establish in the future, any manufacturing facilities or personnel. We rely, and expect to continue to rely, primarily on third parties for the manufacture of our drug candidates for preclinical development and clinical testing, as well as for the commercial manufacture of our current and future drugs. This reliance on third parties increases the risk that we will not have sufficient quantities of our drugs or drug candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

The facilities used by our contract manufacturers to manufacture our drugs and drug candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our marketing applications to the FDA. We do not control the manufacturing process of, and will be completely dependent on, our contract manufacturers for compliance with cGMPs in connection with the manufacture of our drugs and drug candidates. Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to cGMP regulations and applicable product tracking and tracing requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our drugs and drug candidates or is unable to conduct inspections necessary to approve these facilities due to delays or disruptions caused by the ongoing COVID-19 pandemic, or if the FDA or a comparable regulatory authority withdraws any such approval in the future, we may be delayed in obtaining approval of these facilities for the manufacture of our drugs and drug candidates or need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our drug candidates, if approved, and could require comparability studies for the setup of manufacturing operations at alternative facilities. Further, our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of drug candidates or drugs, if approved, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect our business and supplies of our drugs and drug candidates.

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. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches for evaluating public health. Should 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, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. 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.

We do not have long-term supply agreements with all of our contract manufacturers, and may purchase our required drug supply, including the API, drug product and drug substance used in our drugs and drug candidates, on a purchase order basis with certain contract manufacturers. In addition, we may be unable to establish or maintain any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish and maintain agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Any of our drugs and drug candidates that we may develop may compete with other approved drugs and drug candidates for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. In March 2020, the U.S. enacted the CARES Act in response to the U.S. COVID-19 pandemic. Throughout the ongoing COVID-19 pandemic, there has been public concern over the availability and accessibility of critical medical products, and the CARES Act enhances FDA's existing authority with respect to drug shortage measures. Under the CARES Act, we must have in place a risk management plan in place that identifies and evaluates the risks to the supply of approved drugs for certain serious diseases or conditions for each establishment where the drug or API is manufactured. The risk management plan will be subject to FDA review during an inspection.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for all of our bulk drug substances. If our current contract manufacturers cannot perform as agreed, we may experience shortages that require reporting to the FDA or foreign regulatory authorities and may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our approved drugs and drug candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our drugs or drug candidates could result in significant delays or gaps in availability of such drugs or drug candidates and may adversely affect our future profit margins and our ability to commercialize any drugs that receive marketing approval on a timely and competitive basis.

The third parties upon whom we rely for the supply of the API, drug substance and drug product used in avapritinib and pralsetinib are our sole source of supply, and the loss of any of these suppliers could significantly harm our business.

The API, drug substance and drug product used in our drug and drug candidates are supplied to us primarily from single-source suppliers. Our ability to successfully develop our drug candidates, supply our drug candidates for clinical trials and to ultimately supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the API, drug substance and drug product for these drugs in accordance with regulatory requirements and in sufficient quantities for clinical testing and commercialization. Although we have entered into arrangements to establish redundant or second-source supply of some of the API, drug product or drug substance for avapritinib and pralsetinib, if any of our suppliers ceases its operations for any reason or is unable or unwilling to supply API, drug product or drug substance in sufficient quantities or on the timelines necessary to meet our needs, including as a result of the ongoing COVID-19 pandemic, it could significantly and adversely affect our business, the supply of our drug candidates or approved drugs and our financial condition.

For all of our drug candidates, we may from time to time explore opportunities to identify and qualify additional manufacturers to provide such API, drug substance and drug product prior to submission of an NDA to the FDA and/or an MAA to the EMA. We are not certain that our single-source suppliers will be able to meet our demand for their products, either because of the nature of our agreements with those suppliers, our limited experience with those suppliers or our relative importance as a customer to those suppliers. It may be difficult for us to assess their ability to timely meet our demand in the future based on past performance. While our suppliers have generally met our demand for their products on a timely basis in the past, they may subordinate our needs in the future to their other customers. In addition, we currently have sufficient supply or plans for supply to meet our anticipated global commercial and clinical development needs for our approved drugs and clinical-stage drug candidates through 2022. However, the ongoing COVID-19 pandemic could adversely impact our suppliers and result in delays or disruptions in our current or future supply chain.

Establishing additional or replacement suppliers for the API, drug substance and drug product used in our drug candidates or approved drugs, if required, may not be accomplished quickly. If we are able to find a replacement supplier, such replacement supplier would need to be qualified and may require additional regulatory approval, which could result in further delay. While we seek to maintain adequate inventory of the API, drug substance and drug product used in our drug candidates and approved drugs, any interruption or delay in the supply of components or materials, or our inability to obtain such API, drug substance and drug product from alternate sources at acceptable prices in a timely manner could impede, delay, limit or prevent our development efforts, which could harm our business, results of operations, financial condition and prospects.

Certain of our research and development, clinical trials and manufacturing and supply for certain raw materials used in our drugs and our drug candidates takes place in China through third-party CROs, collaborators or manufacturers. A significant disruption in the operation of those CROs, collaborators or manufacturers, could materially adversely affect our business, financial condition and results of operations.

We have relied on certain third parties located in China to manufacture and supply certain raw materials used in our drugs and our drug candidates, and we expect to continue to use such third party manufacturers for such purposes. In addition, certain of our drug candidates are being evaluated at clinical trial sites in China under our collaboration with CStone and through CROs located in China. A natural disaster, epidemic or pandemic disease outbreaks, including the ongoing COVID-19 pandemic, trade war, political unrest or other events in China could disrupt the business or operations of CROs, collaborators, manufacturers or other third parties with whom we conduct business now or in the future. Any disruption in China that significantly impacts such third parties, including services provided by CROs for our research and development programs, clinical trial operations conducted by CROs or our collaborators, or our manufacturers ability to produce raw materials in adequate quantities to meet our needs could impair our ability to operate our business on a day-to-day basis and impede, delay, limit or prevent the research, development or commercialization of our current and future approved drugs or drug candidates. In addition, for any activities conducted in China, we are exposed to the possibility of product supply disruption and increased costs in the event of changes in the policies of the U.S. or Chinese governments, political unrest or unstable economic conditions in China, and we may be exposed to fluctuations in the value of the local currency in China for goods and services. Our costs for any of these services or activities could also increase as a result of future appreciation of the local currency in China or increased labor costs if the demand for skilled laborers increases in China and the availability of skilled labor declines in China.

Risks Related to Intellectual Property

If we are unable to adequately protect our proprietary technology or obtain and maintain patent protection for our technology and drugs or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and drugs similar or identical to ours, and our ability to successfully commercialize our technology and drugs may be impaired.

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection in the U.S. and other countries for our drugs and drug candidates and our core technologies, including our novel target discovery engine and our proprietary compound library and other know-how. We seek to protect our proprietary and intellectual property position by, among other methods, filing patent applications in the U.S. and abroad related to our proprietary compounds, as well as the use of these compounds in the treatment of diseases, formulations, solid state forms, and manufacturing processes and other technologies, inventions and improvements that

are important to the development and implementation of our business. We also rely on copyright, trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

We own or license patents and patent applications that relate to our approved drugs AYVAKIT® (avapritinib) and GAVRETO® (pralsetinib) and our drug candidates fisogatinib, BLU-263, BLU-945, BLU-701, BLU-451 and BLU-222. We also own or license patents and patent applications relating to other compounds that are inhibitors of KIT and PDGFRA, FGFR4, RET, EGFR and CDK2, as well as methods of use, formulations, solid state forms, and manufacturing processes. The issued U.S. patent directed to AYVAKIT® composition of matter has a statutory expiration date in 2034, the issued U.S. patent directed to GAVRETO® composition of matter has a statutory expiration date in 2036.

As of January 31, 2022, the patent portfolio for our KIT and PDGFRA program, including AYVAKIT® and BLU-263 contains 12 issued U.S. patents, 16 issued foreign patents, including one European patent validated in 38 countries, four pending U.S. non-provisional patent applications, three pending U.S. provisional applications, four pending PCT international patent applications and 51 pending foreign patent applications. The patents that have issued or will issue covering our KIT and PDGFRA program will have a statutory expiration date between 2034 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

As of January 31, 2022, the patent portfolio for our RET program, including GAVRETO® contains seven issued U.S. patents, five pending U.S. non-provisional patent applications, two U.S. provisional patent applications, three pending PCT international applications, 58 pending foreign patent applications and nine issued foreign patents. The patents that have issued or will issue covering our RET program will have a statutory expiration date between 2036 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

As of January 31, 2022, the patent portfolio for our FGFR4 program, including fisogatinib contains nine issued U.S. patents, two pending U.S. non-provisional patent applications, one pending PCT international application, 21 pending foreign patent applications and 29 issued foreign patents. The patents that have issued or will issue covering our FGFR4 program will have a statutory expiration date between 2033 and 2040. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

As of January 31, 2022, the patent portfolio for our EGFR program, including BLU-945, BLU-701, and BLU-451 contains one issued U.S. patent, one pending U.S. non-provisional patent application, 13 pending U.S. provisional applications, four pending PCT international patent applications and 14 pending foreign patent applications and two issued foreign patents, including one European patent validated in 6 countries directed to our EGFR program, including BLU-945, BLU-701, and BLU-451. The patents that have issued or will issue covering our EGFR program will have a statutory expiration date between 2034 and 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

As of January 31, 2022, the patent portfolio for our CDK2 program, including BLU-222 contains three pending U.S. provisional applications. The patents that will issue covering our CDK2 program will have a statutory expiration date of 2042. Patent term adjustments, patent term extensions, and supplementary protection certificates could result in later expiration dates.

The intellectual property portfolio directed to our platform includes patents and patent applications directed to novel gene fusions and the uses of these fusions for detecting and treating conditions implicated with these fusions. As of January 31, 2022, the patent portfolio directed to our platform contains eight issued U.S. patents, six pending U.S. non-provisional patent applications, three pending European Union patent applications and six issued European patents. Any U.S. or ex-U.S. patent issuing from the pending applications directed to this technology, if issued, will have statutory expiration dates ranging from 2034 to 2035.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation.

The degree of patent protection we require to successfully commercialize any of our approved drugs and drug candidates may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us

to gain or keep any competitive advantage. We cannot provide any assurances that any of our patents have, or that any of our pending patent applications that mature into issued patents will include, claims with a scope sufficient to protect our drugs and drug candidates. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. Furthermore, patents have a limited lifespan. In the U.S., the natural expiration of a patent is generally twenty years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing drugs similar or identical to our drugs and drug candidates, including generic versions of such drugs or drug candidates.

Other parties have developed technologies that may be related or competitive to our own, and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents, with respect to either the same methods or formulations or the same subject matter, in either case, that we may rely upon to dominate our patent position in the market. 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 not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first-to-file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights cannot be predicted with any certainty. For example, we are aware of patents owned by third parties that have generic composition of matter, method of inhibition and method of treatment claims that may cover fisogatinib or generic method of treatment claims that may cover pralsetinib. If the claims of any of these third-party patents are asserted against us, we do not believe fisogatinib, pralsetinib or our proposed activities related to such compounds would be found to infringe any valid claim of these patents. While we may decide to initiate proceedings to challenge the validity of these patents in the future, we may be unsuccessful, and courts or patent offices in the U.S. and abroad could uphold the validity of any such patents. If we were to challenge the validity of any issued U.S. patent in court, we would need to overcome a statutory presumption of validity that attaches to every U.S. patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent's claims.

In addition, the patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Patent prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, have been significantly narrowed by the time they issue, if at all. 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, there may be circumstances, when we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

Even if we acquire patent protection that we expect should enable us to maintain such competitive advantage, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the U.S. and abroad. For example, we may be subject to a third-party submission of prior art to the USPTO challenging the priority of an invention claimed within one of our patents, which submissions may also be made prior to a patent's issuance, precluding the granting of any of our pending patent applications. We may become involved in opposition, derivation, reexamination, inter partes review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others from whom we have obtained licenses to such rights. Competitors may claim that they invented the inventions claimed in our issued patents or patent applications prior to us or may file patent applications before we do. Competitors may also claim that we are infringing on their patents and that we therefore cannot practice our technology as claimed under our patents, if issued. Competitors may also contest our patents, if issued, by showing the patent examiner that the invention was not original, was not novel or was obvious. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents.

In addition, we may in the future be subject to claims by our former employees, consultants, advisors, and other third parties who have access to our proprietary know-how asserting an ownership right in our patents or patent applications, as a result of the work they performed on our behalf. Although we generally require all of our employees, consultants and advisors and any other third parties who have access to our proprietary know-how, information or technology to assign or grant similar rights to their inventions to us, we cannot be certain that we have executed such agreements with all parties who may have contributed to our intellectual property, nor can we be certain that our agreements with such parties will be upheld in the face of a potential challenge, or that they will not be breached, for which we may not have an adequate remedy.

An adverse determination in any such submission or proceeding 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 drugs, without payment to us, or could limit the duration of the patent protection covering our technology, drugs and drug candidates. Such challenges may also result in our inability to manufacture or commercialize our drugs or drug candidates, if approved, without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future drugs and drug candidates.

Even if they are unchallenged, our issued patents and our pending patents, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our owned or licensed patents by developing similar or alternative technologies or drugs in a non-infringing manner. For example, a third party may develop a competitive drug that provides benefits similar to one or more of our drugs and drug candidates but that has a different composition that falls outside the scope of our patent protection. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our drugs and drug candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our drugs or drug candidates, if approved, could be negatively affected, which would harm our business.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our current and future drugs and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and frequent litigation regarding patents and other intellectual property rights. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our drugs, drug candidates and technology, including interference proceedings before the USPTO. Our competitors or other third parties may assert infringement claims against us, alleging that our drugs are covered by their patents. Given the vast number of patents in our field of technology, we cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Many companies have filed, and continue to file, patent applications related to small molecule therapeutics. Some of these patent applications have already been allowed or issued, and others may issue in the future. For example, we are aware of patents owned by third parties that have generic composition of matter, method of inhibition and method of treatment claims that may cover fisogatinib or generic method of treatment claims that may cover pralsetinib. If the claims of any of these third-party patents are asserted against us, we do not believe fisogatinib, pralsetinib or our proposed activities related to such compounds would be found to infringe any valid claim of these patents. While we may decide to initiate proceedings to challenge the validity of these patents in the future, we may be unsuccessful, and courts or patent offices in the U.S. and abroad could uphold the validity of any such patents. If we were to challenge the validity of any issued U.S. patent in court, we would need to overcome a statutory presumption of validity that attaches to every U.S. patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent's claims.

Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional research and development programs expected in the future. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our drugs and drug candidates. If a patent holder believes any of our approved drugs or drug candidate infringes on its patent, the patent holder may sue us even if we have received patent protection for our drugs,

drug candidates and technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our drug candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby providing our competitors and other third parties access to the same technologies licensed to us. Without such a license, we could be forced, including by court order, to cease developing and commercializing the infringing technology, drugs or drug candidates. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed such third-party patent rights. A finding of infringement could prevent us from commercializing our current and future drugs or force us to cease some of our business operations, which could materially harm our business.

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

Competitors and other third parties may infringe, misappropriate or otherwise violate our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims. A court may disagree with our allegations, however, and may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the third-party technology in question. Further, such third parties could counterclaim that we infringe their intellectual property or that a patent we have asserted against them is invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims challenging the validity, enforceability or scope of asserted patents are commonplace. In addition, third parties may initiate legal proceedings against us to assert such challenges to our intellectual property rights. The outcome of any such proceeding is generally unpredictable. 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. Patents may be unenforceable if someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. It is possible that prior art of which we and the patent examiner were unaware during prosecution exists, which could render our patents invalid. Moreover, it is also possible that prior art may exist that we are aware of but do not believe is relevant to our current or future patents, but that could nevertheless be determined to render our patents invalid.

An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. If a defendant were to prevail on a legal assertion of invalidity or unenforceability of our patents covering any of our approved drugs or drug candidates, we would lose at least part, and perhaps all, of the patent protection covering such drug or drug candidate. Competing drugs may also be sold in other countries in which our patent coverage might not exist or be as strong. If we lose a foreign patent lawsuit, alleging our infringement of a competitor's patents, we could be prevented from marketing our drugs in one or more foreign countries. Any of these outcomes would have a materially adverse effect on our business.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time-consuming and is likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating or from

successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our drugs, drug candidates or procedures, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our drugs or drug candidates, which would have a material adverse effect on our business.

We may not be able to effectively enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our drugs and drug candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. In addition, the patent laws of some foreign countries do not afford intellectual property protection to the same extent as the laws of the U.S. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S. Competitors may use our drugs, drug candidates and technologies in jurisdictions where we have not obtained patent protection to develop their own drugs and, further, may export otherwise infringing drugs to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These drugs may compete with our drugs and drug candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Furthermore, while we intend to protect our intellectual property rights in the major markets for our drugs and drug candidates, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our drug candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Changes to the patent law in the U.S. and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our drugs and drug candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve both technological and legal complexity and is therefore costly, time-consuming and inherently uncertain. Recent patent reform legislation in the U.S. and other countries, including the Leahy-Smith America Invents Act, or Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. In addition, the Leahy-Smith Act has transformed the U.S. patent system into a “first-to-file” system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its

implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business, results of operations and financial condition.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition, there have been recent proposals for additional changes to the patent laws of the U.S. and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

In addition to the protection afforded by patents, we rely upon unpatented trade secret protection, unpatented know-how and continuing technological innovation to develop and maintain our competitive position. With respect to the building of our proprietary compound library, we consider trade secrets and know-how to be our primary intellectual property. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our consultants and employees. We may not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements, however, despite the existence generally of confidentiality agreements and other contractual restrictions. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result. Enforcing a claim that a third party illegally obtained and is using our trade secrets, like patent litigation, is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside the U.S. are sometimes less willing to protect trade secrets.

Our trade secrets could otherwise become known or be independently discovered by our competitors. Competitors could purchase our drugs and drug candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies, drugs, and drug candidates that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected so as to protect our market against competitors' drugs, our competitive position could be adversely affected, as could our business.

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

We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other proprietary information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may in the future be subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement, or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our drugs or drug candidates if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. An inability to incorporate such technologies or features would have a material adverse effect on our business and may prevent us from successfully commercializing our drugs and drug candidates, if approved. In addition, we may lose valuable

intellectual property rights or personnel as a result of such claims. Moreover, any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent sales representatives. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our drugs and drug candidates, if approved, which would have an adverse effect on our business, results of operations and financial condition.

Risks Related to Our Business, including Employee Matters, Managing Growth and Others

Our business, results of operations and future growth prospects could be materially and adversely affected by the ongoing COVID-19 pandemic.

Due to the continued evolution and uncertain global impacts of the ongoing COVID-19 pandemic and the identification of new variants of COVID-19, we cannot precisely determine or quantify the impact this pandemic will have on our business, operations and financial performance. The extent to which the ongoing COVID-19 pandemic may impact our business, results of operations and future growth prospects will depend on a variety of factors and future developments, which are highly uncertain and cannot be predicted with confidence, including the duration, scope and severity of the pandemic, the duration and extent of travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and other countries to contain and treat COVID-19.

For example, public health actions being undertaken globally in response to the ongoing COVID-19 pandemic, including quarantines, stay-at-home, executive and similar government orders and the prioritization of healthcare resources, could adversely impact our business, results of operations and future growth prospects. For ongoing and planned clinical trials, we anticipate and have experienced some temporary delays or disruptions due to the COVID-19 pandemic, including limited or reduced patient access to trial investigators, hospitals and trial sites, delayed initiation of new clinical trial sites and limited on-site personnel support at various trial sites, which could adversely impact our development plans, including the initiation of planned clinical trials, the rate of enrollment and our ability to conduct ongoing clinical trials. There may also be local orders affecting one or more trial sites, which may trigger mandated changes to our clinical trial protocols or temporary suspensions in the affected trial sites. In addition, quarantines, stay-at-home, executive and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations have occurred and could continue to occur or be expanded in scope or duration, which could adversely impact:

- ongoing and planned clinical trials;
- our employees and business operations;
- personnel at our third-party suppliers and other vendors in the U.S. and other countries;
- the availability, cost or supply of materials, which may cause delays or disruptions to development plans for our drug candidates or clinical or commercial supply chains for our current or future approved drugs and drug candidates; and
- sales and marketing activities related to AYVAKIT/AYVAKYT, GAVRETO and any drug candidates for which we may receive marketing approval in the U.S. or other geographies in the future.

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

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

We are highly dependent on the research and development, clinical, commercial, business development, financial and legal expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements with our executive officers, each of our executive officers may terminate their employment with us at any time. In addition, insurance coverage is increasingly expensive, including with respect to directors and officers liability insurance, or D&O insurance. We may

not be able to maintain D&O insurance at a reasonable cost or in an amount adequate to satisfy any liability that may arise. An inability to secure and maintain D&O insurance may make it difficult for us to retain and attract talented and skilled directors and officers to serve our company, which could adversely affect our business. We do not maintain "key person" insurance for any of our executives or other employees.

In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to continue hiring qualified development personnel. Recruiting and retaining qualified scientific, clinical, regulatory, manufacturing and sales and marketing personnel is critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing key employees and executive officers may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize drugs. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

As of January 31, 2022, we had 495 full-time and part-time employees, and we expect to continue to increase our number of employees and expand the scope of our operations. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Physical expansion of our operations in the future may lead to significant costs, including capital expenditures, and may divert financial resources from other projects, such as the development of our drug candidates. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our drug candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the ongoing COVID-19 pandemic has caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our drug candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services.

Political development can also lead to uncertainty to regulations and rules that may materially affect our business. For example, as the UK regulatory system is now independent from the EU, Brexit could result in the UK significantly altering its regulations affecting the clearance or approval of our drug or drug candidates that are developed in the UK. Any new regulations could add time and expense to the conduct of our business, as well as the process by which our drug candidates receive regulatory approval in the UK, as compared to the European Union and elsewhere.

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

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as clinical trial sites or the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, could have a material adverse effect on our business.

Our internal computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our drugs' and drug candidates' development programs and have a material adverse effect on our reputation, business, financial condition or results of operations.

Our internal computer systems and those of our current or future third-party collaborators, service providers, contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized groups and individuals with a wide range of motives and expertise. In addition to extracting sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. The prevalent use of mobile devices also increases the risk of data security incidents. While we have not experienced any material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in a material disruption of our drugs' and drug candidates' development programs and significant reputational, financial, legal, regulatory, business or operational harm. For example, the loss of clinical trial data for our drugs or drug candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or drug candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our drug candidates could be delayed. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyberattacks and other related breaches.

Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations to third parties, or any data security incidents or other security breaches that result in the unauthorized access, release or transfer of sensitive information, including physician data, patient data, or any personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us, could cause third parties to lose trust in us or could result in claims by third parties asserting that we have breached our privacy, confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents.

Interruptions in the availability of server systems or communications with Internet or cloud-based services, or failure to maintain the security, confidentiality, accessibility or integrity of data stored on such systems, could harm our business.

We rely upon a variety of Internet service providers, third-party hosting facilities and cloud computing platform providers to support our business. Failure to maintain the security, confidentiality, accessibility or integrity of data stored on such systems could damage our reputation in the market, cause us to lose revenue or market share, increase our service costs, cause us to incur substantial costs, subject us to liability for damages and/or fines and divert our resources from other tasks, any one of which could materially adversely affect our business, financial condition, results of

operations and prospects. Any damage to, or failure of, such systems, or communications to and between such systems, could result in interruptions in our operations. If our security measures or those of our third-party data center hosting facilities, cloud computing platform providers, or third-party service partners, are breached, and unauthorized access is obtained to our data or our information technology systems, we may incur significant legal and financial exposure and liabilities.

We do not have control over the operations of the facilities of our cloud service providers and our third party providers may be vulnerable to damage or interruption from natural disasters, cybersecurity attacks, terrorist attacks, power outages and similar events or acts of misconduct. In addition, any changes in our cloud service providers' service levels may adversely affect our ability to meet our requirements and operate our business.

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

Privacy and data security have become significant issues in the U.S., Europe and in many other jurisdictions where we conduct or may in the future conduct our operations. The regulatory framework for the collection, use, safeguarding, sharing and transfer of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. Notably, for example, on May 25, 2018, the European General Data Protection Regulation 2016/679, which is commonly referred to as GDPR, took effect. The GDPR applies to any company established in the EEA as well as any company outside the EEA that collects or otherwise processes personal data in connection with the offering goods or services to individuals in the EEA or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on services providers. The GDPR imposes additional obligations and risk upon our business and substantially increase the penalties to which we could be subject in the event of any non-compliance, including fines of up to €20 million or 4% of total worldwide annual turnover, whichever is higher. Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR requirements has required and will continue to require significant time, resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the EEA.

Further, European data protection laws also prohibit the transfer of personal data from the EEA and Switzerland to third countries that are not considered to provide adequate protections are provided for personal data, including the U.S. With regard to transfers of personal data from the EEA, transfers to third countries that have not been approved as "adequate" are prohibited unless an appropriate safeguard specified by the GDPR is implemented, such as the Standard Contractual Clauses, or SCCs, approved by the European Commission or binding corporate rules, or a derogation applies. In 2020, the Court of Justice of the European Union, or the CJEU, deemed that transfers made pursuant to the EU SCCs and other alternative transfer mechanisms, including binding corporate rules, need to be analyzed on a case-by-case basis to ensure EU standards of data protection are met in the jurisdiction where the data importer is based, and there continue to be concerns about whether these transfer mechanisms will face additional challenges. European regulators have issued recent guidance following the CJEU case that imposes significant new diligence requirements on transferring data outside the European Union, including under an approved transfer mechanism. This guidance requires an "essential equivalency" assessment of the laws of the destination country transferred. If essentially equivalent protections are not available in the destination country, the exporting entity must then assess if supplemental measures can be put in place that, in combination with the chosen transfer mechanism, would address the deficiency in the laws and ensure that essentially equivalent protection can be given to the data.

On June 4, 2021, the European Commission issued new SCCs that account for the CJEU's decision and other developments, which need to be put in place for new contracts involving the transfer of personal data from the European Economic Area to a third country as of September 27, 2021, and incorporated into existing contracts by December 27, 2022. Complying with these obligations and applicable guidance regarding cross-border data transfers could be expensive and time consuming, may require us to modify our data handling policies and procedures and may ultimately prevent or restrict us from transferring personal data outside the European Economic Area which could cause significant business disruption.

While we have taken steps to mitigate the impact on us with respect to transfers of data, such as implementing the SCCs in new contracts with our service providers, customers, subsidiaries, and are updating existing contracts with the new SCCs in anticipation of the December 2022 deadline, the validity of these transfer mechanisms remains uncertain. Complying with this guidance as it exists today and evolves will be expensive and time consuming and may ultimately prevent us from transferring personal data outside the European Union, which would cause significant business disruption for ourselves and our customers and potentially require the changes in the way our products are configured, hosted and supported.

In addition, we are subject to Swiss data protection laws, including the Federal Act on Data Protection, or the FADP. While the FADP provides broad protections to personal data, on September 25, 2020, the Swiss federal Parliament enacted a revised version of the FADP, which is anticipated to become effective in 2022 or the beginning of 2023. The new version of the FADP aligns Swiss data protection law with the GDPR.

Further, in addition to existing European data protection law, the European Union also is considering another draft data protection regulation. The proposed regulation, known as the Regulation on Privacy and Electronic Communications, or ePrivacy Regulation, would replace the current ePrivacy Directive. The Draft Regulation is still the subject of negotiations between the Council of the European Union and the European Parliament. An update is expected in 2022. The aim is for the Draft Regulation to be in force some time in 2023. New rules related to the ePrivacy Regulation are likely to include enhanced consent requirements in order to use communications content and communications metadata, as well as obligations and restrictions on the processing of data from an end-user's terminal equipment, which may negatively impact our product offerings and our relationships with our customers.

Preparing for and complying with the evolving application of the GDPR, national laws in Switzerland and the UK, as well as ePrivacy Regulation (if and when it becomes effective) has required and will continue to require us to incur substantial operational costs and may require us to change our business practices. Despite our efforts to bring practices into compliance with the GDPR, appliable national data protection laws and before the effective date of the ePrivacy Regulation, we may not be successful either due to internal or external factors such as resource allocation limitations. Non-compliance could result in proceedings, fines or penalties against us by governmental entities, customers, data subjects, consumer associations or others.

As another prominent example, we are also subject to data protection regulation in the UK. Following the UK's withdrawal from the EU on January 31, 2020 and the end of the transitional arrangements agreed between the UK and EU as of January 1, 2021, the GDPR has been incorporated into UK domestic law by virtue of section 3 of the European Union (Withdrawal) Act 2018 and amended by the Data Protection, Privacy and Electronic Communications (Amendments etc.) (EU Exit) Regulations 2019, or the UK GDPR. United Kingdom-based organizations doing business in the European Union will need to continue to comply with the GDPR. Although the UK is regarded as a third country under the EU's GDPR, the European Commission has now issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing. The UK data protection authority has issued draft guidance on a mechanism governing transfers of personal data from UK to third countries, which incorporates the EU SCCs through an addendum. The aim is for the guidance to be finalised in the first half of 2022. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher. Although the UK is regarded as a third country under the EU's GDPR, the European Commission has now issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing.

In addition to European data protection requirements, we are subject to the California Consumer Privacy Act, or CCPA, which took effect on January 1, 2020 and imposes sweeping privacy and security obligations on many companies doing business in California and provides for substantial fines for non-compliance and, in some cases, a private right of action to consumers who are victims of data breaches involving their unredacted or unencrypted personal information. While there is currently an exception for protected health information that is subject to HIPAA and clinical trial regulations, as currently written, the CCPA may impact our business activities. The CCPA became enforceable as of July 1, 2020, but there continues to be uncertainty about how the law will be interpreted and enforced.

Additionally, a new California ballot initiative, the California Privacy Rights Act, or CPRA, was passed in November 2020. Effective starting on January 1, 2023, the CPRA imposes additional obligations on companies covered by the legislation and 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 effects of the CCPA and the CPRA are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement and/or litigation.

Also, on March 2, 2021, Virginia enacted the Consumer Data Protection Act, or CDPA. The CDPA will become effective January 1, 2023. The CDPA will regulate how businesses, which the CDPA refers to as "controllers", collect and share personal information. The law applies to companies that conduct business in Virginia or product products or services that are targeted to residents of Virginia and either: (1) annually control or process personal data of at least 100,000 Virginia residents; or (2) control or process the personal data of at least 25,000 Virginia residents and derive over 50% of gross revenue from the sale of personal data. While the CDPA incorporates many similar concepts of the CCPA and CPRA, there are also several key differences in the scope, application, and enforcement of the law that will change the operational practices of controllers. The new law will impact how controllers collect and process personal sensitive data, conduct data protection assessments, transfer personal data to affiliates, and respond to consumer rights requests. In addition, on July 8, 2021, Colorado's governor signed the Colorado Privacy Act, or CPA, into law. The CPA is rather similar to the Virginia's CPDA but also contains additional requirements. The new measure applies to companies conducting business in Colorado or who produce or deliver commercial products or services intentionally targeted to its residents of the state and that either: (1) control or process the personal data of at least 100,000 Colorado residents during a calendar year; or (2) derive revenue or receive a discount on the price of goods or services from the sale of personal data and process or control the personal data of at least 25,000 Colorado residents.

With the CPA, Colorado became the third state to enact a comprehensive privacy law but it is quite possible that other states will follow suit and bills have been proposed in many states. We expect anticipate that more states to may enact legislation similar to the CCPA and the other recent consumer privacy laws. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, 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. The existence of comprehensive privacy laws in different states in the country will make our compliance obligations more complex and costly and may increase the likelihood that we may be subject to enforcement actions or otherwise incur liability for noncompliance.

The increasing number and complexity of regional, country and U.S. state data protection laws, and other changes in laws or regulations across the globe, especially those associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could lead to government enforcement actions and significant penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

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

We are exposed to the risk that our employees, principal investigators, CROs and consultants may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate the regulations of the FDA and other regulatory authorities, including those laws requiring the reporting of true, complete and accurate information to such authorities; healthcare fraud and abuse laws and regulations in the U.S. and abroad; or laws that require the reporting of financial information or data accurately. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter misconduct by employees and other third 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. In addition, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. 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 civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We may acquire or in-license businesses, technologies or platforms, approved drugs, drug candidates or discovery-stage programs, or form strategic alliances, collaborations or partnerships, in the future, and we may not realize the benefits of such acquisitions, in-licenses, alliances, collaborations or partnerships.

We may acquire or in-license additional businesses, technologies or platforms, approved drugs, drug candidates or discovery-stage programs, or form strategic alliances, collaborations or partnerships that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new drugs or drug candidates resulting from a strategic alliance, collaboration, partnership or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. In addition, we cannot assure you that, following any such transaction, we will achieve the expected synergies to justify the transaction.

We may be subject to adverse legislative or regulatory tax changes that could negatively impact our 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 IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect our stockholders or us. We assess the impact of various tax reform proposals and modifications to existing tax treaties in all jurisdictions where we have operations to determine the potential effect on our business and any assumptions we have made about our future taxable income. We cannot predict whether any specific proposals will be enacted, the terms of any such proposals or what effect, if any, such proposals would have on our business if they were to be enacted. For tax years beginning after December 31, 2021, the Tax Cuts and Jobs Act of 2017 eliminates the once available option to deduct research and development expenditures currently and requires taxpayers to amortize them over five years. The U.S. Congress is considering legislation that would defer the amortization requirement to future periods; however, we have no assurance that the provision will be repealed or otherwise modified. If the requirement is not repealed or modified, it will have a material impact on our cash flows beginning in 2022.

Risks Related to Our Common Stock

The price of our common stock has been and may in the future be volatile and fluctuate substantially.

Our stock price has been and may in the future be subject to substantial volatility. For example, our stock traded within a range of a high price of $125.61 and a low price of $13.04 per share for the period beginning on April 30, 2015, our first day of trading on The Nasdaq Global Select Market, through February 15, 2022. As a result of this volatility, our stockholders could incur substantial losses.

The stock market in general has recently experienced relatively large price and volume fluctuations, particularly in response to the COVID-19 outbreak. In particular, the market prices of securities of Nasdaq listed and biopharmaceutical companies have experienced extreme fluctuations that often have been unrelated or disproportionate to the operating results of these companies. Continued market fluctuations could result in extreme volatility in the price of our common stock, which could include a decline in the value of our common stock. In addition, the market price for our common stock may be influenced by many factors, including:

- the success of commercialization of our drugs and drug candidates, if approved;
- the success of competitive drugs or technologies;

- results of clinical trials of our drug candidates or those of 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;
- the level of expenses related to any of our drug candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional drug candidates or drugs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- natural disasters, epidemic or pandemic disease outbreaks, including the COVID-19 pandemic, trade wars, political unrest or other similar events;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

Future sales or issuances of common stock or other equity related securities may also adversely affect the market price of our common stock. For example, In July 2020, we entered into a sales agreement with Cowen through which we may, from time to time, issue and sell shares of our common stock having an aggregate offering price of up to $250.0 million, subject to the terms and conditions of the sales agreement. In the year ended December 31, 2020, we issued and sold 1,784,926 shares of our common stock under the sales agreement at an average price of $112.05 per share for net and gross proceeds of $194.7 million and $200.0 million, respectively. We did not sell any shares of common stock under the sales agreement during the year ended December 31, 2021. If we seek authorization to sell additional shares of common stock under the sales agreement, enter into new "at the market" stock offering programs, or conduct a public offering or private offering through other means, it could lead to additional dilution for our stockholders and may impact our stock price adversely.

These and other market and industry factors may cause the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of our management.

If equity research analysts publish negative evaluations of or downgrade our common stock, the price of our common stock could decline.

The trading market for our common stock relies in part on the research and reports that equity research analysts publish about us or our business. We do not control these analysts. If one or more of the analysts covering our business downgrade their evaluations of our common stock, the price of our common stock could decline. If one or more of these analysts cease to cover our common stock, we could lose visibility in the market for our common stock, which in turn could cause our common stock price to decline.

Our executive officers, directors, principal stockholders and their affiliates maintain the ability to exercise significant influence over our company and all matters submitted to stockholders for approval.

Our executive officers, directors and stockholders who own more than 5% of our outstanding common stock, together with their affiliates and related persons, beneficially own shares of common stock representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to influence our management and affairs and the outcome of matters submitted to our stockholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquiror from making a tender offer or otherwise attempting to obtain control of us.

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

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include a classified board of directors, a prohibition on actions by written consent of our stockholders and the ability of our board of directors to issue preferred stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirors to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Our bylaws contain exclusive forum provisions, which may limit a stockholder's ability to bring a claim in a judicial forum it finds favorable and may discourage lawsuits with respect to such claims.

Our amended and restated bylaws, as amended, or 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 state law claims for (1) any derivative action, (2) any claim of breach of fiduciary duty, (3) any claim against a current or former director, officer, employee or stockholder, and (4) any action against our company governed by the internal affairs doctrine, which we refer to collectively as the Delaware forum provision. The Delaware forum provision does not apply to any claims arising under the Securities Exchange Act of 1934 or the Securities Act of 1933, as amended, or the Securities Act. Our bylaws further provide that, unless we consent in writing to an alternative forum, the United States District Court for the District of Massachusetts will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, which we refer to as the federal forum provision. We have chosen the United States District Court for the District of Massachusetts as the exclusive forum for such Securities Act causes of action because our principal executive offices are located in Massachusetts. In addition, our 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 Delaware forum provision and the federal forum provision.

The Delaware forum provision and the federal forum provision may impose additional litigation costs on stockholders who assert the provision is not enforceable and may impose more general additional litigation costs in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts. In addition, these forum selection clauses in our bylaws may limit our stockholders'

ability to bring a claim in a judicial 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. The federal forum provision may also impose additional litigation costs on stockholders who assert the provision is not enforceable or invalid. Alternatively, if the federal forum provision is found inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could have an adverse effect on our business, financial condition or results of operations. The Court of Chancery of the State of Delaware and the United States District Court for the District of Massachusetts 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.

Future sales of our common stock, including by us or our directors and executive officers or shares issued upon the exercise of currently outstanding options, could cause our stock price to decline.

A substantial portion of our outstanding common stock can be traded without restriction at any time. In addition, a portion of our outstanding common stock is currently restricted as a result of federal securities laws, but can be sold at any time subject to applicable volume limitations. As such, sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, by us or others, could reduce the market price of our common stock or impair our ability to raise adequate capital through the sale of additional equity securities. In addition, we have a significant number of shares that are subject to outstanding options. The exercise of these options and the subsequent sale of the underlying common stock could cause a further decline in our stock price. These sales also might make it difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate. We cannot predict the number, timing or size of future issuances or the effect, if any, that any future issuances may have on the market price for our common stock.

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

As a public company, we have incurred and expect to continue to incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the Securities and Exchange Commission, or SEC, and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and make some activities more time-consuming and costlier.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish an annual report by our management on our internal control over financial reporting. To achieve compliance with Section 404 within the prescribed period, we have been and will continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting.

Despite our efforts, there is a risk that in the future neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404 or that we will not be able to comply with the requirements of Section 404 in a timely manner. If this were to occur, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources. Furthermore, investor perceptions of our company may suffer if deficiencies are found, and this could cause a decline in the market price of our stock. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal control over financial reporting from our independent registered public accounting firm.

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

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

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

Under Section 382 of the Internal Revenue Code of 1986, as amended (the Code), if a corporation undergoes an "ownership change" (generally defined as a greater than 50% change (by value) in the ownership of its equity over a three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and certain other pre-change tax attributes to offset its post-change income may be limited. 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. As of December 31, 2021, we had federal net operating loss carryforwards of approximately $872.6 million, and our ability to utilize those net operating loss carryforwards could be limited by an "ownership change" as described above, which could result in increased tax liability to us. In addition, pursuant to the TCJA, we may not use net operating loss carry-forwards generated in taxable years beginning after December 31, 2017 to reduce our taxable income in any year beginning after December 31, 2020 by more than 80%, and we may not carry back any net operating losses to prior years. These rules apply regardless of the occurrence of an ownership change.

With respect to the net operating losses and research and development tax credit carryforwards acquired from the acquisition of Lengo, the Company has not completed a study to assess whether an ownership change under Section 382 of the Code has occurred, or whether there have been multiple ownership changes since Lengo's formation. Accordingly, the Company's ability to utilize the aforementioned carryforwards may be limited and in turn, may not be able to take full advantage of these carryforwards for U.S. federal or state income tax purposes.

Item 1B. Unresolved Staff Comments.

Not applicable.

Item 2. Properties.

Our headquarters are located at 45 Sidney Street in Cambridge, Massachusetts where we occupy approximately 139,216 rentable square feet of office and laboratory space under a lease that will expire on November 30, 2029, unless terminated sooner.

We also lease approximately 39,000 rentable square feet at our former corporate headquarters at 38 Sidney Street in Cambridge, Massachusetts under a lease that was extended on December 15, 2021. The extended lease will expire on November 30, 2029. Since the first quarter of 2018, we have subleased these premises, and the term of the existing subleases will expire on February 28, 2022 and September 30, 2022.

We believe that our existing office and laboratory space is sufficient to meet our needs for the foreseeable future and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol "BPMC" on the Nasdaq Global Select Market and has been publicly traded since April 30, 2015.

Holders

As of January 31, 2022, there were approximately 11 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

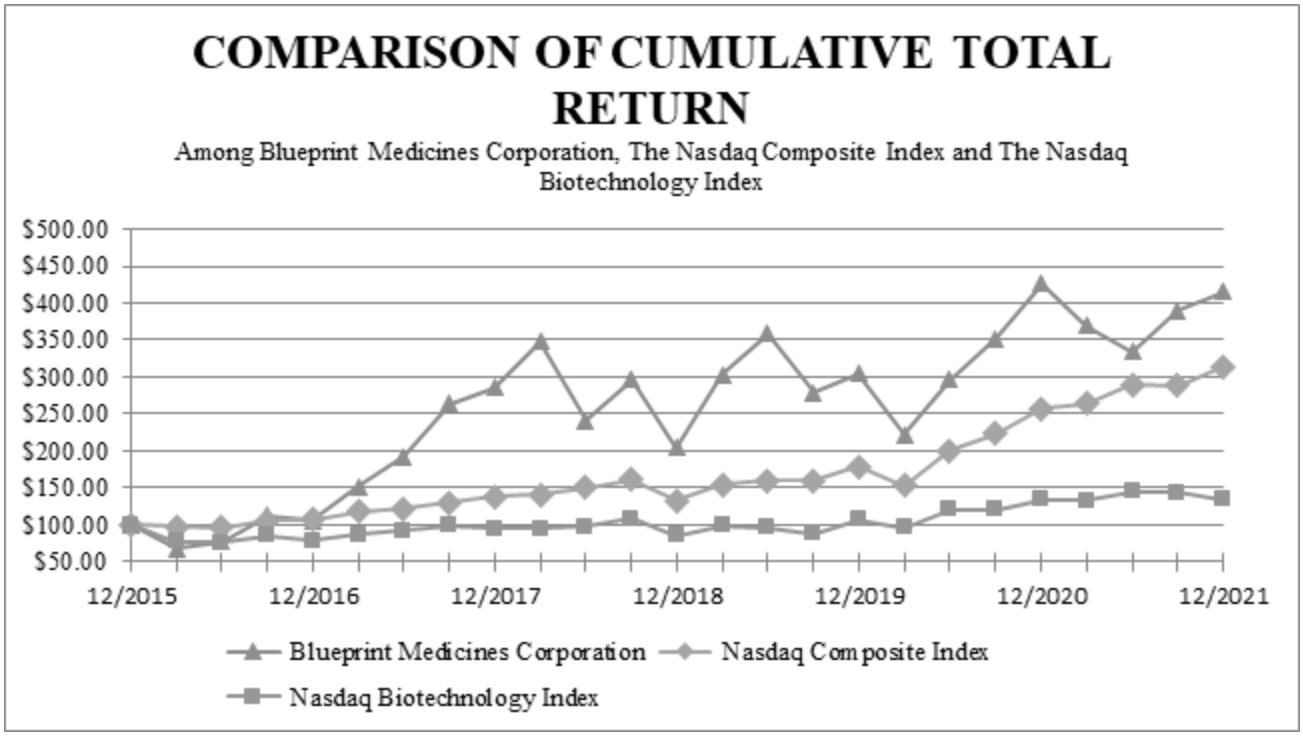
Dividends

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings, if any, 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 pay dividends will be made at the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects and any other factors deemed relevant by our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividend.

Stock Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the Securities and Exchange Commission, or SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, nor shall such information be incorporated by reference into any future filing under the Exchange Act or Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following performance graph compares the performance of our common stock to the Nasdaq Composite Index and to the Nasdaq Biotechnology Index from December 31, 2015 through December 31, 2021. The comparison assumes $100 was invested in our common stock and in each of the foregoing indices after the market closed on December 31, 2015, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of, nor is it intended to forecast, future stock price performance.



Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans 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.

Unregistered Sales of Equity Securities and Use of Proceeds

None.

Recent Sales of Unregistered Equity Securities

None.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

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 audited consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the ''Risk Factors'' section of this Annual Report on Form 10-K, our actual results or timing of certain events could differ materially from the results or timing described in, or implied by, these forward-looking statements.

Information pertaining to fiscal year 2019 was included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020 on pages 86 through 107 under Part II, Item 7, "Management's Discussion and Analysis of Financial Position and Results of Operations," which was filed with the Securities and Exchange Commission (the "SEC") on February 17, 2021.

Overview

We are a global precision therapy company that is inventing life-changing medicines for people with cancer and blood disorders. Applying an approach that is both precise and agile, we create therapies that selectively target genetic drivers, with the goal of staying one step ahead across stages of disease. Since 2011, we have leveraged our research platform, including expertise in molecular targeting and world-class drug design capabilities, to rapidly and reproducibly translate science into a broad pipeline of precision therapies. Today, we are delivering our approved medicines, AYVAKIT®/AYVAKYT® (avapritinib) and GAVRETO® (pralsetinib), to patients in the U.S. and Europe, and we are globally advancing multiple programs for SM, lung cancer and other genomically defined cancers, and cancer immunotherapy.

Our drug discovery approach combines our biological insights with our proprietary compound library and chemistry expertise to design highly selective and potent precision therapies, with the goal of delivering significant and durable clinical benefit to patients based on the genetic driver of their disease. This uniquely targeted, scalable approach is designed to empower the rapid design and development of new treatments and increase the likelihood of success. In addition, our business model integrates our research engine with robust clinical development and commercial capabilities in oncology and hematology to create a cycle of innovation.

Systemic Mastocytosis and other Mast Cell Disorders — AYVAKIT/AYVAKYT (avapritinib) and BLU-263

Avapritinib

We are developing and commercializing avapritinib for the treatment of advanced SM, and developing avapritinib for the treatment of non-advanced SM. SM is a rare hematologic disorder that causes an overproduction of mast cells and the accumulation of mast cells in the bone marrow and other organs, which can lead to a wide range of debilitating symptoms and, in advanced forms of the disease, organ dysfunction and failure. Nearly all cases of SM are driven by the KIT D816V mutation, which aberrantly activates mast cells.

In June 2021, the FDA approved avapritinib under the brand name AYVAKIT for the treatment of adult patients with advanced SM, including ASM, SM-AHN, and MCL. In January 2022, the CHMP of the EMA adopted a positive opinion recommending marketing authorization for avapritinib as a monotherapy for the treatment of adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy. Pending the European Commission's final decision on our MAA, we anticipate obtaining regulatory approval from the EMA and launching avapritinib under the brand name AYVAKYT for advanced SM in Europe in the second quarter of 2022.

In addition, through our distribution agreement with Neopharm Israel Ltd., a marketing authorization application in Israel was submitted in June 2021 for avapritinib for patients with advanced SM and PDGFRA exon 18 mutant GIST. In the future, we plan to pursue the regulatory approval and commercialization of avapritinib in additional global geographies, including through additional potential distribution agreements.

We are evaluating avapritinib in an ongoing registration-enabling Phase 1 clinical trial in advanced SM, which we refer to as our EXPLORER trial, and an ongoing registration-enabling Phase 2 clinical trial in advanced SM, which we refer to as our PATHFINDER trial. In April 2021, we presented registration-enabling data from the PATHFINDER trial at the virtual AACR Annual Meeting.

In addition, we are evaluating avapritinib in an ongoing registration-enabling Phase 2 clinical trial in non-advanced SM, which we refer to as our PIONEER trial. In January 2022, we announced that the PIONEER trial was fully enrolled. We plan to report top-line data for Part 2 of the PIONEER trial in mid-2022 and to submit an sNDA to the FDA for avapritinib in non-advanced SM in the second half of 2022.

The FDA has granted breakthrough therapy designation to avapritinib for (i) the treatment of advanced SM, including the subtypes of ASM, SM-AHN and MCL, and (ii) the treatment of moderate to severe indolent SM. In addition, the FDA has granted orphan drug designation to avapritinib for the treatment of mastocytosis, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of mastocytosis.

BLU-263

We are developing BLU-263, an investigational, orally available, potent and highly selective KIT inhibitor, for the treatment of non-advanced SM and other mast cell disorders. BLU-263 is designed to have equivalent potency as avapritinib, with low off-target activity and lower CNS penetration relative to avapritinib based on preclinical data, which we believe will enable development of BLU-263 in a broad population of patients with non-advanced SM, including patients with lower disease burden and potentially patients with other mast cell disorders.

In April 2021, we presented results from a Phase 1 trial of BLU-263 in healthy volunteers at the virtual AACR Annual Meeting, which showed that BLU-263 was well-tolerated at all doses tested. Based on these data, we initiated the Phase 2/3 HARBOR trial of BLU-263 in patients with non-advanced SM in the second quarter of 2021. We anticipate presenting initial data from the HARBOR trial in the second half of 2022.

RET-Altered Cancers — GAVRETO® (pralsetinib)

We are developing and commercializing pralsetinib for the treatment of RET fusion-positive NSCLC, and for the treatment of RET-altered thyroid carcinoma, including MTC. We are also developing pralsetinib for the treatment of other RET-altered solid tumors. We have granted exclusive licenses to Roche and CStone to develop and commercialize pralsetinib in their respective territories. See "*—Collaborations and Licenses Summary*" below.

Pralsetinib received accelerated approval in the U.S. under the brand name GAVRETO for the treatment of (i) adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test, (ii) adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC who require systemic therapy, and (iii) adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

In November 2021, Roche announced that the European Commission granted conditional marketing authorization for GAVRETO as a monotherapy for the treatment of adults with RET fusion-positive advanced NSCLC not previously treated with a RET inhibitor. Roche submitted a Type II variation MAA to the EMA for pralsetinib for RET-altered thyroid cancers in December 2021, as well as marketing applications for pralsetinib for RET-altered NSCLC and thyroid cancers across multiple global geographies in 2021. Marketing applications are planned for pralsetinib for RET-altered NSCLC and thyroid cancers across additional global geographies in 2022.

In March 2021, China's NMPA approved GAVRETO for the treatment of RET fusion-positive NSCLC patients previously treated with platinum-based chemotherapy. In April 2021, China's NMPA accepted CStone's new drug application, or NDA, with Priority Review designation, for pralsetinib for the treatment of RET-mutant MTC and RET fusion-positive thyroid cancer.

We are currently evaluating pralsetinib in an ongoing registration-enabling Phase 1/2 clinical trial in patients with RET-altered NSCLC, MTC and other advanced solid tumors, which we refer to as the ARROW trial. In addition, Roche is conducting multiple ongoing studies, including a registration-enabling Phase 3 clinical trial in treatment-naïve patients with RET fusion-positive NSCLC, which is referred to as the ACCELERET-Lung trial; and a registration-enabling Phase 3 clinical trial in patients with locally advanced or metastatic RET-mutated MTC who have not previously received a standard of care multi-kinase inhibitor therapy, which is referred to as the ACCELERET-MTC trial. In June 2021, we reported updated data from the ARROW trial in metastatic RET fusion-positive NSCLC and other advanced solid tumors at the 2021 ASCO Annual Meeting. The ARROW trial was fully enrolled in December 2021. Pursuant to our collaboration with Roche, we are co-developing pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, as well as other solid tumors.

The FDA has granted breakthrough therapy designation to pralsetinib for (i) the treatment of patients with RET fusion-positive NSCLC that has progressed following platinum-based chemotherapy, and (ii) the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments. In addition, the FDA has granted orphan drug designation to pralsetinib for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC.

PDGFRA-Driven Gastrointestinal Stromal Tumors — AYVAKIT/ AYVAKYT (avapritinib)

We are commercializing avapritinib for the treatment of patients with PDGFRA exon 18 GIST, a rare disease that is a sarcoma, or tumor of bone or connective tissue, of the gastrointestinal tract. Avapritinib is approved in the U.S. under the brand name AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations, and is approved in Europe with conditional marketing authorization under the brand name AYVAKYT as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring a PDGFRA D842V mutation.

In March 2021, CStone announced that China's NMPA approved AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. AYVAKIT received accelerated approval in April 2021 from the TFDA and approval in Hong Kong in December 2021, both for adults with unresectable or metastatic GIST harboring PDGFRA D842V mutations.

The FDA has granted breakthrough therapy designation for avapritinib for the treatment of unresectable or metastatic GIST harboring the PDGFRA D842V mutation. In addition, the FDA has granted orphan drug designation to avapritinib for the treatment of GIST, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of GIST.

EGFR-Mutated NSCLC — BLU-701, BLU-945 and BLU-451

We are developing three investigational EGFR inhibitors, BLU-701, BLU-945 and BLU-451, which was formerly known as LNG-451, with the goal of addressing the nearly all activating mutations (>90 percent) in EGFR-driven NSCLC. The introduction of EGFR-targeted therapies, including osimertinib, has transformed the care of patients with EGFR-driven NSCLC; however, there remains a significant need for new treatment options designed to prevent a broad range of resistance mechanisms before they emerge, with the goal of prolonging patient benefit. In addition, there are no approved targeted therapies for patients with disease progression following osimertinib, and limited treatment options for patients with EGFR exon 20 insertion-positive NSCLC.

BLU-701 and BLU-945 were specifically designed to provide comprehensive coverage of common activating and on-target resistance mutations, spare wild-type EGFR and other kinases to limit off-target toxicities, and treat or prevent CNS metastases, which occur frequently in patients with EGFR-driven NSCLC. We believe these profiles may enable BLU-701 and BLU-945 to become the backbones of a range of combination strategies with the potential to address important medical needs for patients with EGFR-driven NSCLC, including in early line treatment settings. We plan to develop BLU-701 and BLU-945 in combination with each other and other therapies, including osimertinib, as an initial treatment designed to prevent resistance from emerging. In addition, we plan to develop BLU-701 and BLU-945 as monotherapies in certain biomarker-selected patient populations.

In December 2021, we completed our acquisition of Lengo Therapeutics, Inc., along with its lead compound LNG-451, which we now refer to as BLU-451. BLU-451 is an oral precision therapy in development for the treatment of NSCLC in patients with EGFR exon 20 mutations.

EGFR-Positive NSCLC — BLU-701

BLU-701 is a selective and potent investigational inhibitor of EGFR harboring either the activating L858R or exon 19 deletion mutations combined with the acquired C797S mutation, the most common on-target resistance mutation to osimertinib. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, BLU-701 showed strong and durable inhibition of tumor growth at doses that are EGFR wild-type sparing, and the potential to be used in both first- and second-line settings. BLU-701 indicated significant CNS penetration in preclinical models, with comparable exposure in the plasma and brain, which illustrates its potential to treat or prevent CNS metastases in patients with EGFR-driven tumors. Based on these preclinical data, we initiated a Phase 1/2 trial of BLU-701 in EGFR-mutant NSCLC, which we refer to as our HARMONY trial, in the fourth quarter of 2021. We plan to present initial clinical data from the HARMONY trial in the second half of 2022.

EGFR-Positive NSCLC — BLU-945

BLU-945 is a selective and potent investigational inhibitor of EGFR harboring either the activating L858R or exon 19 deletion mutations combined with the acquired T790M and C797S mutations, the most common on-target resistance mutations to first-generation EGFR inhibitors and osimertinib, respectively. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, BLU-945 demonstrated potent antitumor activity in osimertinib-resistant tumor models, as well as activity in an intracranial patient-derived xenograft model. Both preclinical models harbored activating mutations combined with the T790M and C797S mutations. Based on these preclinical data, we initiated a Phase 1/2 trial of BLU-945 in patients with EGFR-driven NSCLC, which we refer to as our SYMPHONY trial, in the second quarter of 2021. We plan to present initial clinical data from the SYMPHONY trial in the second quarter of 2022.

EGFR-Positive NSCLC — Combinations with BLU-701 and/or BLU-945

Based on their differentiated selectivity profiles and potency against on-target EGFR activating and resistant mutants, we believe BLU-701 and BLU-945 have the potential to become backbone therapies for a range of combination strategies for EGFR-positive NSCLC across multiple treatment lines, potentially including combinations of BLU-701 or BLU-945 with other EGFR therapies or treatment modalities, as well as BLU-701 and BLU-945 together. In preclinical data presented at the virtual AACR Annual Meeting in April 2021, the combination of BLU-945 with either gefitinib or osimertinib showed enhanced antitumor activity when compared with either gefitinib or osimertinib alone. At the BTOG Annual Conference in January 2022, we reported preclinical data supporting the development of BLU-701 and BLU-945 combination therapy in EGFR-driven NSCLC. Based on these results, we plan to develop BLU-701 and BLU-945 in combination with each other and other agents.

EGFR Exon 20 Insertion-Positive NSCLC — BLU-451

BLU-451 is a selective and potent investigational inhibitor under development for the treatment of EGFR exon 20 insertion-positive NSCLC. Based on preclinical data, BLU-451 potently inhibited all common EGFR exon 20 insertion variants with marked selectivity over wild-type EGFR and off-target kinases, and has shown significant CNS penetration. We recently received clearance for an IND application for BLU-451 for EGFR exon 20 insertion-positive NSCLC. In the first quarter of 2022, we plan to initiate a Phase 1/2 trial of BLU-451 in EGFR exon 20 insertion-positive NSCLC, and we expect to present preclinical data for BLU-451 in the second quarter of 2022.

Cyclin E Aberrant Cancers — BLU-222

We are developing an investigational inhibitor, BLU-222, targeting CDK2 for the treatment of patients with cyclin E aberrant cancers. In subsets of patients across multiple cancer types, aberrant CCNE1 hyperactivates CDK2, resulting in cell cycle dysregulation and tumor proliferation. Aberrant CCNE1 has been observed as a primary driver of disease, as well as a mechanism of resistance to CDK4/6 inhibitors and other therapies

At the virtual AACR Annual Meeting in April 2021, we presented preclinical data showing that selective CDK2 inhibition arrested the cell cycle and blocked tumor proliferation in CCNE1-amplified cell lines, and demonstrated robust and sustained antitumor activity in vivo in models of CCNE1-amplified ovarian, breast and gastric cancer. A selective CDK2 inhibitor also showed improved tolerability compared to a pan-CDK inhibitor and chemotherapy, as measured by animal body weight.

We recently received FDA clearance for an IND application for BLU-222 for cyclin E aberrant cancers. We plan to initiate a Phase 1/2 trial of BLU-222 in cyclin E aberrant cancers, which we refer to as our VELA trial, in the first quarter of 2022, and to present preclinical data for BLU-222 in the second quarter of 2022. BLU-222 is being developed as a single agent and in combination with chemotherapy in gyneocological cancers, and in combination with hormonal and the approved CDK 4/6-inhibitor ribociclib for hormone-receptor-positive, HER2-negative breast cancer.

Advanced Cancers — BLU-852

BLU-852 is a selective and potent investigational inhibitor of MAP4K1, a well-characterized immunokinase involved in the regulation of immune cells. Preclinical data presented at the virtual AACR Annual Meeting in April 2021

show that MAP4K1 inhibition enhanced intratumoral immune cell activation, overcame Treg mediated T cell suppression, and reduced tumor burden both as a monotherapy and in combination with checkpoint inhibition. These preclinical data support the continued development of BLU-852. Under our ongoing cancer immunotherapy collaboration, we expect Roche to initiate a Phase 1 trial of BLU-852, as a single agent and in combination with atezolizumab, in advanced cancers in 2023.

Fisogatinib — Hepatocellular Carcinoma

Fisogatinib is an investigational, orally available, potent and highly selective inhibitor that targets FGFR4, a kinase that is aberrantly activated in a defined subset of patients with HCC. Following a strategic evaluation of the evolving HCC treatment landscape and prioritization of resources across our broad precision therapy pipeline, we have decided to deprioritize our clinical development of fisogatinib for the treatment of advanced HCC. We have discontinued further enrollment the Blueprint Medicines-sponsored clinical trial of fisogatinib as a monotherapy and in combination with sugemalimab, an anti-PD-L1 immunotherapy being developed by CStone. CStone continues to retain development and commercial rights to fisogatinib in the CStone territory.

Discovery Platform

We plan to continue to leverage our discovery platform to systematically and reproducibly identify kinases that are drivers of diseases in genomically defined patient populations, and craft drug candidates that potently and selectively target these kinases. In addition, we plan to expand our discovery platform by building capabilities, supported by external collaborations, for targeted protein degradation of both kinase and non-kinase targets in precision oncology, with the goal of advancing transformative therapies to patients and further broadening the significant productivity of our research engine. Beyond the discovery programs described above, we have multiple pre-development candidate programs for undisclosed kinase targets. In 2022, we plan to nominate two development candidates from our discovery programs. We also plan to share our vision for our expanded discovery platform at an R&D Day in the second half of 2022.

Under our immunotherapy collaboration with Roche, we are conducting activities for up to two discovery programs, including BLU-852. See "*—Collaborations and Licenses Summary*" below.

Collaborations and Licenses

Roche—Immunotherapy Collaboration. In March 2016, we entered into a collaboration with Roche to discover, develop and commercialize small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy (including the kinase target MAP4K1, which is believed to play a role in T cell regulation), as single products or possibly in combination with other therapeutics.

Roche—Pralsetinib Collaboration. In July 2020, we entered into a collaboration with Roche to develop and commercialize pralsetinib for the treatment of RET-altered cancers. Under the collaboration, we and Genentech are co-commercializing GAVRETO in the U.S., and Roche has exclusive commercialization rights for pralsetinib outside of the U.S., excluding the CStone territory. We and Roche are also co-developing pralsetinib globally in RET-altered solid tumors, including NSCLC, MTC and other thyroid cancers, and expanding development of pralsetinib in multiple treatment settings.

CStone. In June 2018, we entered into a collaboration with CStone to develop and commercialize avapritinib, pralsetinib and fisogatinib, as well as back-up forms and certain other forms, in the CStone territory either as a monotherapy or as part of a combination therapy.

Clementia. In October 2019, we entered into a license agreement with Clementia Pharmaceuticals, Inc., or Clementia, a wholly-owned subsidiary of Ipsen S.A., and granted Clementia an exclusive, worldwide, royalty-bearing license to develop and commercialize BLU-782, as well as specified other compounds related to the BLU-782 program. BLU-782 is an investigational, orally available, potent and highly selective inhibitor that targets mutant ALK2 in development for the treatment of FOP. The FDA has granted a rare pediatric disease designation, orphan drug designation and fast track designation to BLU-782, each for the treatment of FOP. Clementia initiated patient dosing in a Phase 2 clinical trial of BLU-782, now referred to as IPN60130, in the first quarter of 2022.

Zai Lab. In November 2021, we entered into a collaboration with Zai Lab to develop and commercialize BLU-

701 and BLU-945 for the treatment of EGFR-driven NSCLC in Greater China, including Mainland China, Hong Kong, Macau and Taiwan. The collaboration aims to accelerate and expand global development of BLU-701 and BLU-945.

Mergers & Acquisitions Summary

Lengo Therapeutics. In December 2021, we completed our acquisition of Lengo Therapeutics, Inc., along with its lead compound LNG-451, now known as BLU-451, which is in development for the treatment of NSCLC in patients with EGFR exon 20 insertion mutations. The acquisition also brought additional undisclosed preclinical precision oncology programs and research tools, including a catalog of covalent, highly brain penetrant kinase inhibitors that we plan to add to our proprietary compound library to further enable future drug discovery efforts.

We will continue to evaluate additional collaborations, acquisitions, partnerships and licenses that could maximize the value of our programs and allow us to leverage the expertise of strategic collaborators, partners and licensors, including in additional geographies where we may not have current operations or expertise. We are also focused on engaging in collaborations, acquisitions, partnerships and license agreements to capitalize on or expand our discovery platform.

Note on the COVID-19 Pandemic

Due to the continued evolution and uncertain global impacts of the ongoing COVID-19 pandemic, and the identification of new variants of COVID-19, we cannot precisely determine or quantify the impact this pandemic will have on our business, operations and financial performance. In 2020, we initially established a work-from-home policy for all employees, other than those performing or supporting business-critical activities, such as certain members of our laboratory and facilities staff. Since we implemented this policy in 2020, we have continued to evaluate and update this policy from time to time for each of our locations and field-based employees based on guidance from federal, state and local government authorities and the severity of the pandemic. We currently offer our office-based employees a certain degree of flexibility of in their work location and we intend to maintain this policy for the foreseeable future. For our ongoing and planned clinical trials, while we anticipate and have experienced some delays or disruptions due to the COVID-19 pandemic, in particular with respect to activation of additional clinical trial sites and patient enrollment rates, we have continued to work with any impacted clinical trial sites to ensure study continuity, enable medical monitoring, facilitate study procedures and maintain clinical data and records, including the use of local laboratories for testing and tumor imaging, home delivery of study drug and remote data and records monitoring. In addition, we currently have sufficient supply or plans for supply to meet our anticipated global commercial and clinical development needs for our approved drugs and clinical-stage drug candidates through 2022. However, depending on the duration and impact of the ongoing COVID-19 pandemic on local and global supply chains, our suppliers could be adversely impacted, which may result in delays or disruptions in our current or future supply chain. COVID-19 may also impact and has impacted our commercial activities for AYVAKIT/AYVAKYT and GAVRETO, including patient access to testing and identification. We are committed to continuing to serve the needs of healthcare providers, patients and other stakeholders during this critical time, including by conducting commercial and medical affairs field activities across our portfolio in virtual formats where in-person interactions are not feasible. We will continue to assess the duration, scope and severity of the COVID-19 pandemic as it evolves and the existing and potential impacts on our business, operations and financial performance, and we will continue to work closely with our third-party vendors, collaborators and other parties in order to seek to advance our pipeline of targeted therapies as quickly as possible, while making the health and safety of our employees and their families, healthcare providers, patients and communities a top priority. Please refer to our Risk Factors in Part I, Item 1A of this Annual Report on Form 10-K for further discussion of risks related to the COVID-19 pandemic.

Financial Operations Overview

To date, we have financed our operations primarily through public offerings of our common stock, private placements of our convertible preferred and common stock, collaborations and a license agreement. Through December 31, 2021, we have received an aggregate of $3.0 billion from such transactions, including $1.9 billion in aggregate gross proceeds from the sale of common stock in our initial public offering, or IPO, follow-on public offerings, through our “at the market” stock offering program and the equity investment by Roche, $115.1 million in gross proceeds from the issuance of convertible preferred stock, $996.3 million in upfront and milestone payments under our collaborations with Roche, CStone and Zai Lab, our license agreement with Clementia and our former collaboration

with Alexion Pharma Holding, or Alexion. In addition, since January 2020, we have also generated revenue through the sales of our approved drug products.

Since inception, we have incurred significant operating losses, with the exception of the year ended December 31, 2020. Our net loss was $644.1 million for the year ended December 31, 2021. Our net income was $313.9 million for the year ended December 31, 2020 primarily due to the collaboration revenue recorded under our collaboration with Roche for pralsetinib. As of December 31, 2021, we had an accumulated deficit of $1,275.4 million. We expect to continue to incur significant expenses and operating losses over the next few years. We anticipate that our expenses will continue to increase in connection with our ongoing activities, particularly as we:

- maintain and expand our sales, marketing and distribution infrastructure to continue to commercialize our drug and any current or future drug candidates for which we may obtain marketing approval;
- seek marketing approval for our drug candidates, including avapritinib and pralsetinib in additional indications or avapritinib in additional geographies;
- continue to advance clinical development activities for avapritinib and pralsetinib and initiate or advance clinical development activities for other current or future drug candidates;
- continue to discover, validate and develop additional drug candidates or development candidates, including BLU-701, BLU-945, BLU-451 and BLU-222;
- continue to manufacture increasing quantities of drug substance and drug product material for use in preclinical studies, clinical trials and commercialization;
- conduct development and commercialization activities for companion diagnostic tests for our drugs and drug candidates;
- conduct research and development activities under our collaborations with Roche, CStone and Zai Lab;
- maintain, expand and protect our intellectual property portfolio;
- acquire or in-license additional businesses, technologies, drugs or drug candidates, form strategic alliances or create joint ventures with third parties; and
- hire additional research, clinical, quality, manufacturing, regulatory, commercial and general and administrative personnel.

Revenue

In January 2020, the FDA granted approval of avapritinib under the brand name AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. In September 2020, the European Commission granted conditional marketing authorization to AYVAKYT as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation. In June 2021, the FDA granted a subsequent approval for AYVAKIT, expanding the labeled indications to include adult patients with advanced SM, including aggressive SM, SM with an associated hematological neoplasm and mast cell leukemia.

In September 2020, the FDA granted accelerated approval to pralsetinib under the brand name GAVRETO for the treatment of adult patients with metastatic RET fusion-positive NSCLC as detected by an FDA approved test. In December 2020, the FDA granted a subsequent accelerated approval for GAVRETO, expanding the labeled indications to include adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant MTC who require systemic therapy, or with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

For the year ended December 31, 2021, our revenue mainly consisted of product sales of our drugs as well as collaboration revenue under our collaborations with Roche, CStone and Zai Lab. We recorded net product revenue from the U.S. product sales of GAVRETO through June 30, 2021, and on July 1, 2021, we transferred certain responsibilities associated with product sales to customers, pricing and distribution matters related to U.S. product sales of GAVRETO to Roche and did not record any net product revenue from product sales of GAVRETO during the second half of 2021. Products sales of GAVRETO were reflected as part of collaboration loss sharing in the consolidated financial statements. For additional information, see Note 11, *Collaboration and License Agreements*, to our consolidated financial statements included in this Form 10-K. Collaboration revenue for the year ended December 31, 2021 primarily includes amounts that were recognized related to milestone and upfront payments, amounts due to us for supply of inventory (under our collaboration agreements) and research and development services, and royalties on drug sales.

In the future, we expect to generate revenue from a combination of sources, including sales of our current drug product and any current or future drug candidates for which we receive marketing approval, royalties on drug sales, upfront, milestone, profit sharing and other payments, if any, under any current or future collaborations and licenses, including revenues related to the supply of our drug candidates or approved drugs to our various collaboration partners. We expect that any revenue we generate will fluctuate from quarter to quarter as a result of the timing and amount of product sales, license fees, research and development services, payments for manufacturing services, and option fees, milestone payments or other payments under our collaboration or license agreements, if any.

Cost of sales

Our cost of sales includes the cost of producing and distributing inventories that are related to product revenue as well as the sales of drug substance and drug product to our collaboration partners during the respective period, including salary related expenses and stock-based compensation expense for employees involved with production and distribution, freight, and indirect overhead costs. In addition, shipping and handling costs for product shipments are recorded in cost of sales as incurred.

Prior to receiving the initial FDA approval for AYVAKIT and GAVRETO in January 2020 and September 2020, respectively, and subsequent approval for AYVAKIT in June 2021, we manufactured inventory to be sold upon commercialization and recorded approximately $37.7 million related to this inventory as research and development expense. As a result, the manufacturing costs related to the inventory build-up incurred before FDA approval were expensed in a prior period and are therefore excluded from the cost of goods sold for the years ended December 31, 2021 and 2020. We estimate our cost of goods sold related to product revenue as a percentage of net product revenue will continue to be positively impacted as we sell through certain inventory that was previously expensed prior to FDA approval. We expect to utilize low cost inventory for an extended period of time. Cost of goods sold related to sales of drug products to our collaboration partners are at lower margins and will partially offset the positive impact of the previously expensed inventory.

Expenses

Collaboration Loss Sharing

On July 1, 2021, Roche took over certain responsibilities associated with product sales to customers, pricing and distribution matters related to GAVRETO in the U.S. and became the principal for recording product sales to customers in the U.S. Collaboration loss sharing consists of our share of the losses incurred from sales of GAVRETO to customers in the U.S. under our collaboration for pralsetinib with Roche. For additional information, see Note 11, *Collaboration and License Agreements*, to our consolidated financial statements included in this Form 10-K. We expect collaboration loss sharing will fluctuate from quarter to quarter as a result of the timing and amount of GAVRETO sales.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research and development activities, including our drug discovery efforts, and the development of our drug candidates, which include:

- expenses incurred to acquire in-process research and development asset with no alternative future use;

- employee-related expenses including salaries, benefits, and stock-based compensation expense;
- expenses incurred under agreements with third parties that conduct research and development, preclinical activities, clinical activities and manufacturing on our behalf;
- expenses incurred under agreements with third parties for the development and commercialization of companion diagnostic tests;
- expenses incurred in connection with research and development activities under our immunotherapy collaboration with Roche, and development activities under our collaboration for pralsetinib with Roche;
- the cost of consultants in connection with our research and development activities;
- the cost associated with regulatory quality assurance and quality control operations;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical study materials, clinical trial materials and commercial supply materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other operating costs in support of research and development activities.

Research and development costs are expensed as incurred. Costs for certain activities are recognized based on an evaluation of the progress to completion of specific tasks. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

The successful development of our drug candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development of these drug candidates. We are also unable to predict when, if ever, material net cash inflows will commence from the sale of our current or future drug candidates for which we received marketing approval. This is due to the numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- establishing an appropriate safety profile with IND-enabling toxicology studies;
- successful initiation, enrollment in, and completion of clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for AYVAKIT/AYVAKYT, GAVRETO and our drug candidates;
- commercializing AYVAKIT/AYVAKYT, GAVRETO and our drug candidates, if and when approved, whether alone or in collaboration with others;
- market acceptance of AYVAKIT/AYVAKYT, GAVRETO and any future drug we may commercialize; and
- continued acceptable safety profile of the drugs following approval.

A change in the outcome of any of these variables with respect to the development of any of our drug candidates would significantly change the costs and timing associated with the development of that drug candidate.

Research and development activities are central to our business model. Drug candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our drug candidate development programs progress and as we conduct and continue our clinical trials to evaluate our approved drugs for additional indications. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through commercialization. There are numerous factors associated with the successful commercialization of any of our approved drugs or drug candidates for which we may receive marketing approval, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development. In addition, future commercial and regulatory factors beyond our control will impact our clinical development programs and plans.

A significant portion of our research and development expenses have been external expenses, which we track on a program-by-program basis following nomination as a development candidate. Our internal research and development expenses are primarily personnel-related expenses, including stock-based compensation expense. Except for internal research and development expenses related to collaboration agreements, we do not track our internal research and development expenses on a program-by-program basis as they are deployed across multiple projects under development.

The following table summarizes our external research and development expenses by program for the years ended December 31, 2021 and 2020. Other development and pre-development candidate expenses, unallocated expenses and internal research and development expenses have been classified separately.

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Avapritinib external expenses	$ 59,355	$ 77,074
Pralsetinib external expenses	29,118	63,066
Fisogatinib external expenses	2,985	4,190
BLU-263 external expenses	22,219	14,138
BLU-701/945 external expenses	47,325	14,549
BLU-222 external expenses	14,353	3,192
BLU-451 external expenses	259,957	—
Other development and pre-development candidate expenses and unallocated expenses	59,609	52,217
Internal research and development expenses	106,112	98,434
Total research and development expenses	$ 601,033	$ 326,860

* Pralsetinib external expenses includes reimbursable expenses under our collaboration for pralsetinib with Roche, and other development and pre-development candidate expenses includes reimbursable expenses under our other collaboration agreements.

We expect that our research and development expenses will increase in future periods as we expand our operations and incur additional costs in connection with our clinical trials and preparing regulatory filings. These increases will likely include the costs related to the implementation and expansion of clinical trial sites and related patient enrollment, monitoring, program management and manufacturing expenses for active pharmaceutical ingredient, or API, drug product and drug substance for current and future clinical trials and commercial inventory. In addition, we expect that our research and development expenses will increase in future periods as we incur additional costs in connection with research and development activities under our immunotherapy collaboration with Roche, development activities under our collaboration for pralsetinib with Roche and development activities for companion diagnostic tests for any current and future drug candidates.

Selling, General and Administrative Expenses

Selling, general and administrative expenses consist primarily of compensation and benefits, including stock-based compensation, for commercial operations and for personnel in executive, finance, accounting, commercial, business development, information technology, legal and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, commercial development activities, legal fees related to intellectual property and corporate matters and fees for accounting and consulting services.

We expect that our selling, general and administrative expenses will continue to increase in the future to support additional research and development activities and commercialization activities, including expanding our sales, marketing and distribution infrastructure to commercialize any drugs for which we may obtain marketing approval for additional indications or in additional geographies and expanding our operations globally. These increases will likely include increased costs related to the hiring of additional personnel, legal, auditing and filing fees and general compliance and consulting expenses, among other expenses. We have incurred and will continue to incur additional costs associated with operating as a public company and expanding the scope of our operations.

Interest Income (Expense), net

Interest income (expense), net consists primarily of income earned on cash equivalents and investments.

Other Income (Expense), net

Other income (expense), net consists primarily of foreign currency transaction gains or losses.

Income Tax Expense

Income tax expense consists primarily of income taxes related to our product sales in the state jurisdictions where we conduct business and foreign withholding income taxes incurred.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make judgments and estimates that affect the reported amounts of assets, liabilities, revenues, 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 are believed to be reasonable under the circumstances. Some of those judgments can be subjective and complex, and consequently actual results could differ from those estimates. For any given individual estimate or assumption we make, it is possible that other people applying reasonable judgment to the same facts and circumstances could develop different estimates. We believe that, given current facts and circumstances, it is unlikely that applying any such other reasonable judgment would cause a material adverse effect on our consolidated results of operations, financial position, or liquidity for the periods presented in this report. We evaluate our judgments and estimates in light of changes in circumstances, facts and experience on an ongoing basis.

Critical accounting estimates are those estimates that, in accordance with generally accepted accounting principles, involve a significant level of estimation uncertainty and have had or are reasonably likely to have a material impact on our consolidated financial statements. Management has determined that our most critical accounting estimates are those relating to revenue recognition, accrued research and development expenses and acquisitions. We have reviewed our critical accounting estimates with our audit committee. For further discussion about our general accounting policies, see Note 2 *Summary of Significant Accounting Policies and Recent Accounting Pronouncements,* to our consolidated financial statements included in the Form 10-K.

Revenue Recognition

We recognize revenue when we transfer control of goods or services to our customers. Revenue is measured as the amount of consideration we expect to receive in exchange for goods and services. We generate revenue from product sales and revenue transactions with our collaboration partners.

Product Revenue

For product sales to customers, provisions for returns, rebates and discounts are established in the same period the related product sales are recognized. To determine the appropriate transaction price for our product sales at the time we recognize a sale to a direct customer, we estimate any rebates, chargebacks or discounts that ultimately will be due to the direct customer and other customers in the distribution chain under the terms of our contracts. Significant judgments are required in making these estimates. The largest of our sales rebate and discount amounts are rebates associated with sales covered by Medicare, Medicaid, and chargeback contracts in the U.S. We utilize the expected value method to determine the appropriate amount for estimates based on factors such as historical rebate payments for these programs, the current contractual and statutory requirements, specific known market events and sales trends, industry data and forecasted customer buying and payment patterns, the percentage of our products that are sold via these programs, and our product pricing. Actual amounts of consideration ultimately received may differ from our estimates. If actual results vary from our estimates, we adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Collaboration Revenue

Revenue recognized from collaborations and other arrangements will include royalties on drug sales, upfront, milestone, profit sharing and other payments, if any, under any current or future collaborations and licenses, including revenues related to the supply of our drug candidates or approved drugs to our various collaboration partners under these types of contracts.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our vendors in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to research and development activities on our estimates of the services received and efforts expended pursuant to quotes and contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it

could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

Acquisitions

To determine whether acquisitions or licensing transactions should be accounted for as a business combination or as an asset acquisition, we make certain judgments, which include assessing whether the acquired set of activities and assets would meet the definition of a business under the relevant accounting rules.

If the acquired set of activities and assets meets the definition of a business, assets acquired and liabilities assumed are required to be recorded at their respective fair values as of the acquisition date. The excess of the purchase price over the fair value of the acquired net assets, where applicable, is recorded as goodwill. If the acquired set of activities and assets does not meet the definition of a business, the transaction is recorded as an acquisition of assets and, therefore, any acquired in-process research and development assets that does not have an alternative future use is charged to research and development expense at the acquisition date, and goodwill is not recorded.

The judgments made in determining estimated the fair values of the identifiable intangible assets acquired, the assigned to assets acquired and liabilities assumed in a business combination, as well as estimated asset lives, can materially affect our consolidated results of operations. The fair values of intangible assets, including acquired in-process research and development assets, are determined using information available near the acquisition date based on estimates and assumptions that are deemed reasonable by management. Significant estimates and assumptions include, but are not limited to, probability of technical success, revenue growth and discount rate. When significant identifiable intangible assets are acquired, we generally engage an independent third-party valuation firm to assist in determining the fair values of these assets.

Results of Operations

Comparison of Years Ended December 31, 2021 and 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020, together with the changes in those items in dollars and as a percentage.

	Year Ended December 31,			
	2021	2020	Dollar Change	% Change
		(in thousands)		
Revenues:				
Product revenue, net	$ 57,687	$ 22,134	$ 35,553	161 %
Collaboration revenue	122,393	771,601	(649,208)	(84)
Total revenue	180,080	793,735	(613,655)	(77)
Cost and operating expenses:				
Cost of sales	17,934	425	17,509	4,120
Collaboration loss sharing	7,801	—	7,801	100
Research and development	601,033	326,860	274,173	84
Selling, general and administrative	195,293	157,743	37,550	24
Total cost and operating expenses	822,061	485,028	337,033	69
Other income (expense):				
Interest income, net	2,386	6,599	(4,213)	(64)
Other expense, net	(1,489)	(366)	1,123	307
Total other income (expense)	897	6,233	(5,336)	(86)
Income (loss) before income taxes	(641,084)	314,940	(956,024)	(304)
Income tax expense	3,001	1,058	1,943	184
Net income (loss)	$ (644,085)	$ 313,882	$ (957,967)	(305)%

Product Revenue, Net

Product revenue, net increased by $35.6 million from $22.1 million for the year ended December 31, 2020 to $57.7 million for the year ended December 31, 2021.

We started generating revenue from sales of AYVAKIT in the first quarter of 2020 following FDA approval of AYVAKIT for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. In September 2020, the European Commission granted conditional marketing authorization to avapritinib under the brand name AYVAKYT as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation. In June 2021, the FDA granted a subsequent approval for AYVAKIT, expanding the labeled indications to include adult patients with advanced SM, including aggressive SM, SM with an associated hematological neoplasm and mast cell leukemia.

We started generating revenue from sales of GAVRETO in the third quarter of 2020 following the initial FDA approval of GAVRETO. GAVRETO was originally approved for the treatment of adult patients with metastatic RET fusion-positive NSCLC and subsequently approved for adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). We recorded net product revenue from the U.S. product sales of GAVRETO through June 30, 2021, and on July 1, 2021, we transferred certain responsibilities associated with product sales to customers, pricing and distribution matters related to U.S. product sales of GAVRETO to our collaboration partner and did not record any net product revenue from product sales of GAVRETO during the second half of 2021. Products sales of GAVRETO were reflected as part of collaboration loss sharing in the consolidated financial statements. For additional information, see Note 11*, Collaboration and License Agreements*, to our consolidated financial statements included in the Form 10-K.

The following table summarizes revenue recognized from sales of AYVAKIT/AYVAKIT and GAVRETO during the years ended December 31, 2021, and 2020 (in thousands):

	Year Ended December 31,					
	2021			2020		
	United States	Rest of World	Total	United States	Rest of World	Total
AYVAKIT/AYVAKYT	$ 44,959	$ 8,022	$ 52,981	$ 20,522	$ 740	$ 21,262
GAVRETO	4,706	—	4,706	872	—	872
Total product revenue, net	$ 49,665	$ 8,022	$ 57,687	$ 21,394	$ 740	$ 22,134

Collaboration Revenue

Collaboration revenue decreased by $649.2 million from $771.6 million for the year ended December 31, 2020 to $122.4 million for the year ended December 31, 2021. The following table summarizes the revenue recognized from our collaboration and license agreements during the years ended December 31, 2021 and 2020 (in thousands):

	Year Ended December 31,	
	2021	2020
Collaboration with Roche for pralsetinib	$ 56,022	$ 753,100
CStone collaboration	33,395	3,630
Zai Lab collaboration	25,000	—
Cancer immunotherapy with Roche	7,636	14,580
Other	340	291
Total collaboration and license revenue	$ 122,393	$ 771,601

Revenue recognized under our collaboration with Roche for pralsetinib for the year ended December 31, 2021 consisted of $50.0 million in specified regulatory milestone payments and $6.0 million associated with services related to Roche territory-specific activities. Revenue recognized under our CStone collaboration for the year ended December 31, 2021 primarily consisted of $24.4 million associated with royalties on drug sales and the manufacturing services related to CStone territory-specific activities during the year, including supply of drug products to CStone for sale in their territory, and $9.0 million in milestone revenue related to development milestones that were achieved during the year. Revenue recognized under our Zai Lab collaboration for the year ended December 31, 2021 consisted of a $25.0 million upfront cash payment. We recognized $7.6 million in revenue under our cancer immunotherapy collaboration with Roche for the year ended December 31, 2021, which was primarily related to the amortization of the total $68.5 million of upfront and milestone payments received as of such period.

Revenue recognized under our collaboration with Roche for pralsetinib for the year ended December 31, 2020 consisted of $695.7 million upfront cash payment including the $20.7 million premium associated with the $100.0 million equity investment by Roche, $55.0 million in specified regulatory and commercialization milestone payments and $2.4 million associated with services related to Roche territory-specific activities. Revenue recognized under our CStone collaboration for the year ended December 31, 2020 primarily consisted of $2.0 million in milestone revenue related to a development and regulatory milestones that were achieved during the year and $1.6 million associated with drug supply related to CStone territory-specific activities. We recognized $14.6 million in revenue under our cancer immunotherapy collaboration with Roche for the year ended December 31, 2020, which was primarily related to the amortization of the total $64.5 million of upfront and milestone payments received during such period.

Cost of Product Sales

Cost of sales increased by $17.5 million from $0.4 million for the year ended December 31, 2020 to $17.9 million for the year ended December 31, 2021 and was related to manufacturing costs associated with our product sales

as well as costs associated with the sale of drug product to our collaboration partners. The following table summarizes the cost of sales by type during the years ended December 31, 2021 and 2020 (in thousands):

	Year Ended December 31,	
	2021	2020
Cost of product sales	$ 3,958	$ 425
Cost of collaboration sales	13,976	—
Total cost of sales	$ 17,934	$ 425

The increase in costs of product sales was primarily driven by the lower margin product sales to our collaboration partners. Costs associated with product revenue, net remain at higher margins as costs associated with the manufacture of our drugs prior to FDA approval were recorded as research and development expenses and, therefore, were not included in cost of sales during such period.

Collaboration Loss Sharing

Our loss sharing under the collaboration with Roche for pralsetinib was $7.8 million for the year ended December 31, 2021.

Research and Development Expense

Research and development expense increased by $274.2 million from $326.9 million for the year ended December 31, 2020 to $601.0 million for the year ended December 31, 2021. The increase in research and development expense was primarily related to $260.0 million incurred to acquire in-process research and development compounds through the acquisition of Lengo, an increase of approximately $8.6 million in costs related to early discovery efforts, a decrease of $9.3 million in reimbursement from the global development cost sharing arrangement under our collaboration with Roche for pralsetinib, as well as increased costs and personnel expenses, including an increase of $6.0 million in stock-based compensation expense. These increases in research and development expense were primarily offset by a decrease of $8.8 million in expenses associated with the manufacturing of clinical supply.

Selling, general and Administrative Expense

Selling, general and administrative expense increased by $37.6 million from $157.7 million for the year ended December 31, 2020 to $195.3 million for the year ended December 31, 2021. The increase in selling, general and administrative expense was primarily related to increased costs and personnel expenses, including an increase of $10.1 million in stock-based compensation expense, as well as an increase of $17.1 million in commercial expenses to expand our commercial infrastructure for commercialization of AYVAKIT/AYVAKYT and GAVRETO. The increase in selling, general and administrative expense was partially offset by $8.1 million increase in reimbursement in connection with the commercialization of GAVRETO in the U.S. under our collaboration with Roche for pralsetinib.

Interest Income, Net

Interest income, net decreased by $4.2 million from $6.6 million for the year ended December 31, 2020 to $2.4 million for the year ended December 31, 2021. The decrease was primarily due to a combination of lower cash, cash equivalents and marketable securities balance and lower rate of return on investments in the capital markets.

Other Expense, Net

Other expense, net increased by $1.1 million from $0.4 million for the year ended December 31, 2020 to $1.5 million for the year ended December 31, 2021. The increase was primarily related to changes in foreign currency exchange rates.

Income Tax Expense

Income tax expense increased by $1.9 million from $1.1 million for the year ended December 31, 2020 to $3.0 million for the year ended December 31, 2021. The increase was primarily related to an increase in foreign withholding income tax, which is partially offset by a decrease in state income taxes in 2021.

Liquidity and Capital Resources

Sources of Liquidity

To date, we have financed our operations primarily through public offerings of our common stock, private placements of our convertible preferred and common stock, collaborations and a license agreement. Through December 31, 2021, we have received an aggregate of $3.0 billion from such transactions, including $1.9 billion in aggregate gross proceeds from the sale of common stock in our IPO, follow-on public offerings, through our "at the market" stock offering program and the equity investment by Roche, $115.1 million in gross proceeds from the issuance of convertible preferred stock, $996.3 million in upfront payments and milestone payments under our collaborations with Roche and CStone, Zai Lab and our license agreement with Clementia and our former collaboration with Alexion. In addition, since January 2020, we have generated limited product revenue.

As of December 31, 2021, we had cash, cash equivalents and marketable securities of $1,034.6 million.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2021, 2020 and 2019:

	Year Ended December 31,	
(in thousands)	**2021**	**2020**
Net cash provided by (used in) operating activities	$ (298,653)	$ 387,035
Net cash used in investing activities	(225,860)	(434,249)
Net cash provided by financing activities	50,716	617,759
Net increase (decrease) in cash and cash equivalents	$ (473,797)	$ 570,545

Net Cash Provided by (Used in) Operating Activities. For the year ended December 31, 2021, compared to the same period in 2020, the $685.7 million decrease in net cash provided by operating activities was primarily due to a $958.0 million decrease in net income. During the year ended December 31, 2020, the Company had a net income of $313.9 million which was driven by the $753.1 million collaboration revenue recognized under our collaboration agreement with Roche for pralsetinib.

Net Cash Used in Investing Activities. For the year ended December 31, 2021, compared to the same period in 2020, the $208.4 million decrease in net cash used in investing activities was primarily due to a $466.5 million decrease in net purchases of available-for-sale investments offset by $258.1 million of cash used to acquire an in-process research and development asset.

Net Cash Provided by Financing Activities. For the year ended December 31, 2021, compared to the same period in 2020, the $567.0 million decrease in net cash provided by financing activities was primarily due to the $503.2 million in proceeds received from our common stock offerings net of issuance costs and the $79.3 million received from the issuance of common stock related to the collaboration agreement with Roche for Pralsetinib in 2020, partially offset by a $15.5 million increase in net proceeds received from stock option exercises and the issuance of common stock under our employee stock purchase plan.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate or continue clinical trials of, and seek marketing approval for our drug candidates,

including marketing approval for avapritinib and pralsetinib for additional indications or avapritinib in additional geographies, to the extent these expenses are not the responsibility of our collaborators. In addition, we expect to incur additional significant commercialization expenses for AYVAKIT/AYVAKYT, GAVRETO and other drug candidates, if approved, related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of potential collaborators or licensors. We will also incur additional significant costs if we choose to pursue additional indications or geographies for any of our approved drugs or drug candidates or otherwise expand more rapidly than we presently anticipate. Accordingly, we may seek to obtain additional funding from time to time in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate certain of our research and development programs or future commercialization efforts.

As of December 31, 2021, we had cash, cash equivalents and marketable securities of $1,034.6 million. Based on our current operating plans, we anticipate our existing cash, cash equivalents and marketable securities, together with anticipated future product revenues, will provide sufficient capital to enable us to achieve a self-sustainable financial profile.

Our future capital requirements will depend on many factors, including:

- the success of our commercialization efforts and market acceptance for AYVAKIT/AYVAKYT, GAVRETO or any of our current or future drug candidates for which we receive marketing approval;
- the costs of maintaining, expanding or contracting for sales, marketing and distribution capabilities in connection with commercialization of AYVAKIT/AYVAKYT and any of our current or future drug candidates for which we receive marketing approval;
- the costs of securing manufacturing, packaging and labeling arrangements for development activities and commercial production, including API, drug substance and drug product material for use in preclinical studies, clinical trials, our compassionate use program and for use as commercial supply, as applicable;
- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our approved drugs and drug candidates;
- the costs, timing and outcome of regulatory review of marketing applications for our drug candidates, including seeking marketing approval for avapritinib and pralsetinib for additional indications or avapritinib in additional geographies;
- the success of our collaborations with Roche, CStone and Zai Lab and our license agreement with Clementia, as well as our ability to establish and maintain additional collaborations, partnerships or licenses on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under our existing collaboration or license agreements, or any collaboration, partnership or license agreements that we may enter into in the future;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, research and development, clinical or other costs under future collaboration agreements, if any;
- the extent to which we acquire or in-license other approved drugs, drug candidates or technologies and the terms of any such arrangements;
- the success of our current or future collaborations for the development and commercialization of companion diagnostic tests;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and

- the costs of continuing to expand our operations.

Identifying potential drug candidates, conducting preclinical development and testing and clinical trials and, for any drug candidates that receive marketing approval, establishing and maintaining commercial infrastructure is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain additional marketing approvals, including for avapritinib and pralsetinib in additional indications or avapritinib in additional geographies, and achieve substantial revenues for any of our drugs that receive marketing approval, including for AYVAKIT/AYVAKYT and GAVRETO. In addition, our drugs and any current or future drug candidates that receive marketing approvals, including avapritinib and pralsetinib for additional indications or avapritinib in additional geographies, may not achieve commercial success. Accordingly, we may need to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial drug revenues, we expect to finance our cash needs primarily through a combination of public and private equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations with Roche, CStone and Zai Lab and the license agreement with Clementia, which are limited in scope and duration and subject to the achievement of milestones or royalties on sales of licensed products, if any. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that materially adversely affect the rights of our common stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Contractual Obligations

We have entered into arrangements that contractually obligate us to make payments that will affect our liquidity and cash flows in future periods. Our contractual obligations primarily consist of our obligations under non-cancellable operating leases and unconditional purchase obligations related to certain commercial manufacturing agreements. The aggregate amount of future minimum purchase obligations under these manufacturing agreements over the period of next five years is approximately $34.2 million as of December 31, 2021, of which $16.7 million are expected to be paid within one year. The aggregate amount of future operating lease obligations over the term of our leases, excluding net sublease receivables, is $148.3 million as of December 31, 2021. For additional information on our leases and timing of future payments, see Note 16, *Leases*, to the consolidated financial statements included in this Form 10-K.

In the normal course of business, we enter into agreements with contract research organizations for clinical trials and clinical supply manufacturing and with vendors for preclinical research studies, synthetic chemistry and other services and products for operating purposes. We have not included these payments in the contractual obligations above since the contracts are generally cancelable at any time by us upon less than 180 days' prior written notice. Certain of these agreements require us to pay milestones to such third parties upon achievement of certain development, regulatory or commercial milestones. Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent on the successful achievement of certain development, regulatory approval and commercial milestones, which may not be achieved.

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain milestones, including future payments to third parties with whom we have entered into agreements to develop and commercialize companion diagnostic tests for certain of our drug candidates. We have not

included these commitments on our balance sheet or in the contractual obligations above because the achievement and timing of these milestones is not fixed and determinable.

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, *Summary of Significant Accounting Policies and Recent Accounting Pronouncements*, to our consolidated financial statements included in this Form 10-K.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

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

As of December 31, 2021 and 2020, we had cash, cash equivalents and marketable securities of $1,034.6 million and $1,549.7 million, respectively, consisting primarily of money market funds and investments in U.S. government agency securities and treasury obligations.

Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, including recent changes resulting from the impact of the COVID-19 pandemic. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we believe an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio. We have the ability to hold our investments until maturity, and therefore, we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates, including recent changes resulting from the impact of the COVID-19 pandemic. From time to time, we contract with vendors that are located in Asia and Europe, which are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2021 and 2020, we held limited funds and future obligations denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor, clinical trial and manufacturing costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2021 and 2020.

Item 8. Financial Statements and Supplementary Data.

The financial statements and the report of our independent registered public accounting firm (PCAOB ID:42) required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15 of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures

Management's Evaluation of our Disclosure Controls and Procedures

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms and (2) accumulated and communicated to our management, including our principal executive and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. Based upon such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2021, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, a company's principal executive officer and principal financial officer, or persons performing similar functions, and effected by a company's board of directors, management, and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of a company's assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that a company's receipts and expenditures are being made only in accordance with authorizations of the company's management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision of and with the participation of our principal executive officer and principal financial officer, our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2021 based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control—Integrated Framework (2013 framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2021.

Our independent registered public accounting firm has issued an attestation report of our internal control over financial reporting. This report appears below.

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors of Blueprint Medicines Corporation

Opinion on Internal Control Over Financial Reporting

We have audited Blueprint Medicines Corporation's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework) (the COSO criteria). In our opinion, Blueprint Medicines Corporation (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of Blueprint Medicines Corporation as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive income (loss), stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes and our report dated February 17, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP
Boston, Massachusetts
February 17, 2022

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

At-the-Market Offering Agreement

On February 17, 2022, we entered into a sales agreement with Cowen and Company, LLC, or Cowen, pursuant to which we may offer and sell, from time to time at our sole discretion, shares of our common stock, par value $0.001 per share, having an aggregate offering price of up to $300.0 million through Cowen as sales agent. Cowen may sell the shares under such sales agreement by any method that is deemed to be an "at the market offering" as defined in Rule 415 of the Securities Act of 1933, as amended, including sales made directly on the Nasdaq Global Select Market or any other trading market for our common stock. Cowen will use commercially reasonable efforts to sell the shares from time to time, based upon instructions from us (including any price, time or size limits or other customary parameters or conditions we may impose). We will pay Cowen a commission of up to 3.0% of the gross sales proceeds of any common stock sold through Cowen under the sales agreement, and we have also provided Cowen with customary indemnification rights. We are not obligated to make any sales of our common stock under the sales agreement. The offering of shares of our common stock pursuant to the sales agreement will terminate upon the earlier of (i) the sale of all common stock subject to the sales agreement or (ii) the termination of the sales agreement in accordance with its terms.

The foregoing description of the sales agreement is qualified in its entirety by reference to the complete text of such agreement, a copy of which is attached hereto as Exhibit 1.1 to this Annual Report on Form 10-K and incorporated herein by reference. The legal opinion of Goodwin Procter LLP relating to the shares of our common stock being offered pursuant to the sales agreement is filed as Exhibit 5.1 to this Annual Report on Form 10-K.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item 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 and Financial Statement Schedules.

(1) Financial Statements

The following documents are included on pages F-1 through F-39 attached hereto and are filed as part of this Annual Report on Form 10-K.

Report of Independent Registered Public Accounting Firm F-2
Consolidated Balance Sheets F-5
Consolidated Statements of Operations and Comprehensive Income (Loss) F-6
Consolidated Statements of Stockholders' Equity F-7
Consolidated Statements of Cash Flows F-8
Notes to Consolidated Financial Statements F-10

(2) Financial Statement Schedules

Schedules have been omitted since they are either not required or not applicable or the information is otherwise included herein.

(3) Exhibits

Exhibit Number	Description of Exhibit	Incorporated by Reference			Filing Date
		Form	File No.	Exhibit Number	
1.1	Sales Agreement, dated as of February 17, 2022, by and between Blueprint Medicines Corporation and Cowen and Company, LLC				*
2.1~††	Agreement and Plan of Merger by and among the Company, Pavonis Merger Subsidiary, Inc., Lengo Therapeutics, Inc. and Fortis Advisors, LLC, dated November 27, 2021	8-K	001-37359	2.1	December 30, 2021
3.1	Fifth Amended and Restated Certificate of Incorporation of the Registrant	10-Q	001-37359	3.1	November 9, 2015
3.2	Amended and Restated Bylaws, as amended on April 30, 2020, of the Registrant	10-Q	001-37359	3.1	May 6, 2020
4.1	Specimen Common Stock Certificate	S-1/A	333-202938	4.1	April 20, 2015
4.2	Second Amended and Restated Investors' Rights Agreement, dated as of November 7, 2014, by and among the Registrant and the Investors listed therein	S-1	333-202938	4.4	March 23, 2015
4.3	Description of the Registrant's securities registered pursuant to Section 12 of the Securities and Exchange Act of 1934, as amended	10-K	001-37359	4.3	February 13, 2020
5.1	Opinion of Goodwin Procter LLP				*
10.1#	2011 Stock Option and Grant Plan, as amended, and forms of award agreements thereunder	S-1	333-202938	10.1	March 23, 2015
10.2#	2015 Stock Option and Incentive Plan and forms of award agreements thereunder	10-K	001-37359	10.2	February 13, 2020
10.3#	2015 Employee Stock Purchase Plan	10-K	001-37359	10.3	February 13, 2020

10.4#	2020 Inducement Plan and form of award agreements thereunder	S-8	333-238039	99.1	May 6, 2020
10.5	Lease Agreement, dated February 11, 2015, by and between the Registrant and 38 Sidney Street Limited Partnership	S-1	333-202938	10.4	March 23, 2015
10.6	First Amendment to Lease Agreement, dated January 26, 2018, by and between the Registrant and 38 Sidney Street Limited Partnership	10-K	001-37359	10.5	February 26, 2019
10.7	Second Amendment to Lease Agreement, dated April 6, 2021, by and between Blueprint Medicines Corporation and BRE-BMR 38 SIDNEY LLC	10-Q	001-37359	10.1	April 29,2021
10.8	Third Amendment to Lease Agreement, dated December 15, 2021, by and between Blueprint Medicines Corporation and BRE-BMR 38 SIDNEY LLC				*
10.9	Lease Agreement, dated April 28, 2017, by and between the Registrant and UP 45/75 Sidney Street, LLC	10-Q	001-37359	10.1	May 3, 2017
10.10	First Amendment of Lease, dated September 19, 2018, between Blueprint Medicines Corporation and UP 45/75 Sidney Street, LLC	8-K	001-37359	10.1	September 25, 2018
10.11#	Employment Agreement, dated November 6, 2015, by and between the Registrant and Jeffrey W. Albers	10-Q	001-37359	10.2	November 9, 2015
10.12#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Jeffrey W. Albers	8-K	001-37359	10.1	December 23, 2021
10.13#	Amended and Restated Employment Agreement, dated January 4, 2022 and effective as of April 4, 2022, by and between the Registrant and Jeffrey W. Albers	8-K	001-37359	10.1	January 5, 2022
10.14#	Employment Agreement, dated November 6, 2015, by and between the Registrant and Anthony L. Boral	10-Q	001-37359	10.4	November 9, 2015
10.15#	First Amendment to Employment Agreement, dated January 11, 2021, by and between Blueprint Medicines Corporation and Anthony L. Boral, M.D., Ph.D.	8-K	001-37359	10.1	January 11, 2021
10.16#	Employment Agreement, dated March 10, 2016, by and between the Registrant and Kathryn Haviland	10-K	001-37359	10.9	March 11, 2016
10.17#	First Amendment to Employment Agreement, dated January 30, 2019, by and between the Registrant and Kathryn Haviland	8-K	001-37359	10.2	February 5, 2019
10.18#	Second Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Kathryn Haviland	8-K	001-37359	10.4	December 23, 2021

10.19#	Amended and Restated Employment Agreement, dated January 4, 2022 and effective as of April 4, 2022, by and between the Registrant and Kathryn Haviland	8-K	001-37359	10.2	January 5, 2022
10.20#	Employment Agreement, dated September 6, 2016, by and between the Registrant and Tracey L. McCain	10-Q	001-37359	10.3	November 10, 2016
10.21#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Tracey L. McCain	8-K	001-37359	10.5	December 23, 2021
10.22#	Employment Agreement, dated November 9, 2016, by and between the Registrant and Marion Dorsch	8-K	001-37359	10.1	November 14, 2016
10.23#	Employment Agreement, dated October 10, 2017, by and between the Registrant and Christopher Murray	10-Q	001-37359	10.1	October 31, 2017
10.24#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Christopher Murray	8-K	001-37359	10.8	December 23, 2021
10.25#	Employment Agreement, dated November 22, 2017, by and between the Registrant and Michael Landsittel	8-K	001-37359	10.1	November 22, 2017
10.26#	First Amendment to Employment Agreement, dated January 30, 2019, by and between the Registrant and Michael Landsittel	8-K	001-37359	10.1	February 5, 2019
10.27#	Second Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Michael Landsittel	8-K	001-37359	10.2	December 23, 2021
10.28#	Employment Agreement, dated October 29, 2018, by and between the Registrant and Christina Rossi	8-K	001-37359	10.1	October 29, 2018
10.29#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Christina Rossi	8-K	001-37359	10.6	December 23, 2021
10.30#	Amended and Restated Employment Agreement, dated January 4, 2022 and effective as of April 4, 2022, by and between the Registrant and Christina Rossi	8-K	001-37359	10.3	January 5, 2022
10.31#	Employment Agreement, dated March 6, 2019, by and between the Registrant and Ariel Hurley	8-K	001-37359	10.1	March 8, 2019
10.32#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Ariel Hurley	8-K	001-37359	10.11	December 23, 2021
10.33#	Employment Agreement, dated November 22, 2017, by and between the Registrant and Debra Durso-Bumpus, as amended by the First Amendment to Employment Agreement, dated February 10, 2020, by and between the Registrant and Debra Durso-Bumpus	10-K	001-37359	10.19	February 13, 2020

10.34#	Second Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Debra Durso-Bumpus	8-K	001-37359	10.10	December 23, 2021
10.35#	Employment Agreement, effective September 1, 2020, by and between the Registrant and Fouad Namouni, M.D.	8-K	001-37359	10.1	September 1, 2020
10.36#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Fouad Namouni	8-K	001-37359	10.3	December 23, 2021
10.37#	Amended and Restated Employment Agreement, dated January 11, 2021, by and between the Registrant and Becker Hewes, M.D.	8-K	001-37359	10.2	January 11, 2021
10.38#	First Amendment to Amended and Restated Employment Agreement, dated December 22, 2021, by and between the Registrant and Becker Hewes	8K	001-37359	10.7	December 23, 2021
10.39#††	Employment Agreement, effective as of May 19, 2021, by and between the Registrant and Percy Carter	10-Q	001-37359	10.1	July 29, 2021
10.40#	First Amendment to Employment Agreement, dated December 22, 2021, by and between the Registrant and Percy H. Carter	8-K	001-37359	10.9	December 23, 2021
10.41#	Amended and Restated Employment Agreement, dated January 19, 2022 and effective as of April 4, 2022, by and between the Registrant and Philina Lee	8K	001-37359	10.1	January 20, 2022
10.42†	Collaboration and License Agreement, effective March 14, 2016, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant, as amended by Amendment to Collaboration and License Agreement, effective April 15, 2016	10-Q/A	001-37359	10.2	July 22, 2016
10.43†	Second Amendment to Collaboration and License Agreement, effective April 27, 2016, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-Q	001-37359	10.1	August 9, 2016
10.44	Third Amendment to Collaboration and License Agreement, effective August 4, 2016, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-Q	001-37359	10.1	November 10, 2016
10.45†	Fourth Amendment to Collaboration and License Agreement, effective February 25, 2019, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-K	001-37359	10.26	February 26, 2019
10.46††	Fifth Amendment to Collaboration and License Agreement, effective June 28, 2019, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	8-K	001-37359	10.1	July 3, 2019

10.47††	Sixth Amendment to Collaboration and License Agreement, effective November 1, 2019, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-Q	001-37359	10.2	November 5, 2019
10.48††	Seventh Amendment to Collaboration and License Agreement, effective December 17, 2019, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	8-K	001-37359	10.1	December 20, 2019
10.49††	Eighth Amendment to Collaboration and License Agreement, effective April 30, 2020, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-Q	001-37359	10.1	May 6, 2020
10.50††	Ninth Amendment to Collaboration and License Agreement, effective January 8, 2021, by and among F. Hoffmann-La Roche Ltd, Hoffmann-La Roche Inc. and the Registrant	10-K	001-37359	10.32	February 17, 2021
10.51††	Collaboration Agreement, dated as of July 13, 2020, by and among F. Hoffmann-La Roche Ltd, Genentech, Inc. and the Registrant	10-Q	001-37359	10.1	July 30, 2020
10.52†	License and Collaboration Agreement, dated June 1, 2018, between the Registrant and CStone Pharmaceuticals	10-Q	001-37359	10.1	August 1, 2018
10.53††	License Agreement, effective October 15, 2019, by and between the Registrant and Clementia Pharmaceuticals, Inc.	10-Q	001-37359	10.1	November 5, 2019
10.54~††	Collaboration and License Agreement, dated November 8, 2021, by and between the Registrant and Zai Lab (Shanghai) Co. Ltd				*
10.55	Form of Indemnification Agreement entered into between the Registrant and its directors	S-1	333-202938	10.11	March 23, 2015
10.56	Form of Indemnification Agreement entered into between the Registrant and its officers	S-1	333-202938	10.12	March 23, 2015
10.57	Senior Executive Cash Incentive Bonus Plan	10-K	001-37359	10.15	March 11, 2016
21.1	Subsidiaries of the Registrant				*
23.1	Consent of Ernst & Young LLP				*
23.2	Consent of Goodwin Procter LLP (contained in its opinion filed as Exhibit 5.1 and incorporated herein by reference)				*
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				*
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Exchange Act, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				*
32.1+	Certifications of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				+

101.INS	XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL Document	*
101.SCH	XBRL Taxonomy Extension Schema Document	*
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document	*
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document	*
101.LAB	XBRL Taxonomy Extension Label Linkbase Document	*
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document	*
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.*)	

# Indicates management contract or compensatory plan or arrangement.

~ Certain schedules and exhibits to the Agreement have been omitted pursuant to Item 601(a)(5) of Regulation S-K. A copy of any omitted schedule and/or exhibit will be furnished to the Securities and Exchange Commission upon request

† Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

††Certain portions of the exhibit have been omitted pursuant to Regulation S-K Item 601(b) because it is both (i) not material to investors and (ii) likely to cause competitive harm to the Company if publicly disclosed.

* Filed herewith.

+ The certifications furnished in Exhibit 32.1 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 Exchange Act. Such certifications will not be deemed to be incorporated by reference into any filing under the Securities Act or the Exchange Act, except to the extent that the Registrant specifically incorporates it by reference.

Item 16. Form 10-K Summary.

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

BLUEPRINT MEDICINES CORPORATION

Date: February 17, 2022

By: /s/ Jeffrey W. Albers
Jeffrey W. Albers
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/ Jeffrey W. Albers Jeffrey W. Albers	President, Chief Executive Officer and Chairman of the Board *(Principal Executive Officer)*	February 17, 2022
/s/ Michael Landsittel Michael Landsittel	Chief Financial Officer *(Principal Financial Officer)*	February 17, 2022
/s/ Ariel Hurley Ariel Hurley	Vice President, Finance and Controller *(Principal Accounting Officer)*	February 17, 2022
/s/ Nicholas Lydon Nicholas Lydon, Ph.D.	Director	February 17, 2022
/s/ Alexis Borisy Alexis Borisy	Director	February 17, 2022
/s/ Mark Goldberg Mark Goldberg, M.D.	Director	February 17, 2022
/s/ Charles A. Rowland, Jr. Charles A. Rowland, Jr.	Director	February 17, 2022
/s/ George Demetri George Demetri, M.D.	Director	February 17, 2022
/s/ Lonnel Coats Lonnel Coats	Director	February 17, 2022
/s/ Lynn Seely Lynn Seely, M.D.	Director	February 17, 2022
/s/ Daniella Beckman Daniella Beckman	Director	February 17, 2022

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Blueprint Medicines Corporation

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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Blueprint Medicines Corporation

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Blueprint Medicines Corporation as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive income (loss), stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 17, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

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

Accrued Clinical Trial Expenses

Description of the Matter	As discussed in Note 2 to the consolidated financial statements, the Company records costs for clinical trial activities based upon estimates of costs incurred through the balance sheet date that have yet to be invoiced by the contract research organizations and other vendors. Auditing the Company's accruals for clinical trials is challenging due to the fact that information necessary to estimate the accruals is accumulated from multiple sources. In addition, in certain circumstances, the determination of the nature and level of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the level of services provided and there

may be delays in invoicing from clinical study sites and other vendors.

How We Addressed the Matter in Our Audit

We obtained an understanding of, evaluated the design and tested the operating effectiveness of internal controls that addressed the identified risks related to the Company's process for recording accrued clinical expenses.

To evaluate the accrual for clinical expenses, our audit procedures included, among others, testing the completeness and accuracy of the underlying data used in the estimates and evaluating the significant assumptions including, but not limited to, expected patient enrollment, costs per patient, site activation and estimated project duration, that are used by management to estimate the recorded accruals. To assess the reasonableness of the significant assumptions, we corroborated the progress of clinical trials with the Company's clinical team and obtained information directly from third parties related to active patient sites and currently enrolled patients. We also tested subsequent invoicing received from such third parties and inspected the Company's contracts with third parties and any pending change orders to assess the impact to the accrual through the balance sheet date and compared that to the Company's estimates.

Collaboration Agreement with Zai Lab

Description of the Matter

As discussed in Note 11 to the consolidated financial statements, the Company recognized $25.0 million in revenue under the collaboration agreement with Zai Lab (Shanghai) Co., Ltd., ("Zai Lab").

The Company determined that agreement contained two material components: (i) licenses granted to Zai Lab to exploit and develop each licensed product in the Zai Lab territory and related activities in the Zai Lab territory, including manufacturing, and (ii) the parties' participation in the global development of the licensed products. The Company accounts for the licenses and related activities pursuant to ASC 606, Revenue from Contracts with Customers, and the global development activities under ASC 808, Collaborative Arrangements.

The Company evaluated the Zai Lab territory specific licenses and related activities under ASC 606 as these transactions are considered transactions with a customer and identified three material promises at the outset of the Zai Lab agreement, which consists of the following for each licensed product: (1) the exclusive license, (2) the initial know-how transfer and (3) manufacturing activities related to development and commercial supply of the licensed product in the Zai Lab territory.

Auditing management's identification of the material promises were challenging as the contract includes implicit and explicit goods and services. Significant judgment was required in the evaluation of the identification of the promises.

How We Addressed the Matter in Our Audit

We obtained an understanding of, evaluated the design and tested the operating effectiveness of internal controls that addressed the identified risks related to the Company's process for identifying material promises in its contracts.

To test the identification of material promises , we assessed, among other things, the stated terms of the Company's arrangement with Zai Lab. We also conducted meetings with personnel at the Company responsible for negotiating the contract and overseeing the delivery of the components in order to understand the nature as well as understand whether they were capable of being distinct in the context of the contract. Finally, we assessed the Company's analyses to support their conclusion of the amount of revenue to recognize in 2021.

Lengo Therapeutics Inc. Acquisition

Description of the Matter

As described in Note 3 to the Company's consolidated financial statements, the Company completed the acquisition of all the outstanding shares of Lengo Therapeutics Inc. ("Lengo")

for upfront consideration of $250.0 million, subject to customary net indebtedness, transaction expenses, and other adjustments and future contingent cash milestone payments of up to $215.0 million, upon achievement of specified regulatory approval and sales milestones. The acquisition was accounted for as an acquisition of assets that did not meet the definition of a business. The asset acquisition did not constitute a business as substantially all of the fair value of the gross assets acquired was concentrated in Lengo's lead compound LNG-451, now known as BLU-451. The acquired assets and liabilities were recorded at their relative fair values and the Company immediately expensed the acquired intellectual property in the consolidated statement of operations and comprehensive loss in the amount of $260.0 million as the acquired assets represent in-process research and development with no alternative future use.

Auditing management's conclusion that substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets and therefore the Lengo acquisition should be accounted for as an asset acquisition required significant auditor judgment.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of management's controls over the identification and aggregation of the Lengo assets acquired and the application of the qualitative and quantitative considerations in applying the accounting guidance.

To test the Lengo asset acquisition conclusion, our audit procedures included, among others, reviewing the agreement between the Company and Lengo and other information to determine the completeness of identified assets acquired. We assessed the reasonableness of the qualitative and quantitative considerations utilized when determining if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets by comparing it to evidence obtained about Lengo and its legacy operations. As part of our testing of the assessment made by management, we evaluated the reasonableness of the significant assumptions used in the Company's estimate of the gross fair value of the assets acquired. We involved our valuation professionals to assist with our evaluation of the methodology used by the Company and significant assumptions included in the fair value estimates.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2011.

Boston, Massachusetts
February 17, 2022

Blueprint Medicines Corporation
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 209,948	$ 684,636
Marketable securities	267,166	187,213
Accounts receivable	25,155	7,096
Unbilled accounts receivable	11,875	18,213
Inventory	21,817	8,581
Prepaid expenses and other current assets	18,064	22,020
Total current assets	554,025	927,759
Marketable securities	557,529	677,873
Property and equipment, net	30,700	34,129
Operating lease right-of-use assets, net	90,162	67,539
Restricted cash	5,171	5,168
Other assets	14,638	5,925
Total assets	$ 1,252,225	$ 1,718,393
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	8,333	4,370
Accrued expenses	121,829	105,938
Current portion of operating lease liabilities	8,093	7,935
Current portion of deferred revenue	11,510	12,559
Total current liabilities	149,765	130,802
Operating lease liabilities, net of current portion	103,315	81,669
Deferred revenue, net of current portion	25,066	28,599
Other long-term liabilities	3,344	7,235
Total liabilities	281,490	248,305
Commitments and Contingencies (Note 18)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.001 par value; 120,000,000 shares authorized; 59,141,086 and 57,793,533 shares issued and outstanding at December 31, 2021 and December 31, 2020, respectively	59	58
Additional paid-in capital	2,250,250	2,106,600
Accumulated other comprehensive loss	(4,133)	(5,214)
Accumulated deficit	(1,275,441)	(631,356)
Total stockholders' equity	970,735	1,470,088
Total liabilities and stockholders' equity	$ 1,252,225	$ 1,718,393

The accompanying notes are an integral part of the consolidated financial statements.

Blueprint Medicines Corporation
Consolidated Statements of Operations and Comprehensive Income (Loss)
(in thousands, except per share data)

	Year Ended December 31,		
	2021	2020	2019
Revenues:			
Product revenue, net	$ 57,687	$ 22,134	$ —
Collaboration revenue	122,393	771,601	66,512
Total revenues	180,080	793,735	66,512
Cost and operating expenses:			
Cost of sales	17,934	425	—
Collaboration loss sharing	7,801	—	—
Research and development	601,033	326,860	331,450
Selling, general and administrative	195,293	157,743	96,388
Total cost and operating expenses	822,061	485,028	427,838
Other income (expense):			
Interest income, net	2,386	6,599	13,732
Other expense, net	(1,489)	(366)	(100)
Total other income	897	6,233	13,632
Income (loss) before income taxes	(641,084)	314,940	(347,694)
Income tax expense	3,001	1,058	—
Net income (loss)	$ (644,085)	$ 313,882	$ (347,694)
Other comprehensive income (loss):			
Unrealized gain (loss) on pension benefit obligations	4,255	(2,843)	(2,985)
Unrealized gain (loss) on available-for-sale investments	(3,649)	441	671
Currency translation adjustments	475	(278)	(40)
Comprehensive income (loss)	$ (643,004)	$ 311,202	$ (350,048)
Net income (loss) per share — basic	$ (11.01)	$ 5.76	$ (7.27)
Net income (loss) per share — diluted	$ (11.01)	$ 5.59	$ (7.27)
Weighted-average number of common shares used in net income (loss) per share — basic	58,518	54,534	47,829
Weighted-average number of common shares used in net income (loss) per share — diluted	58,518	56,168	47,829

The accompanying notes are an integral part of the consolidated financial statements.

Blueprint Medicines Corporation
Consolidated Statements of Stockholders' Equity
(in thousands)

	Common Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Stockholders'
	Shares	Amount	Capital	Loss	Deficit	Equity
Balance at December 31, 2018	44,037,026	$ 44	$ 1,016,689	$ (180)	$ (597,544)	$ 419,009
Issuance of common stock under stock plan	552,311	1	12,130	—	—	12,131
Purchase of common stock under ESPP	20,724	—	1,148	—	—	1,148
Stock-based compensation expense	—	—	54,653	—	—	54,653
Follow on offering, net of issuance costs	4,662,162	4	327,462	—	—	327,466
Other comprehensive loss	—	—	—	(2,354)	—	(2,354)
Net income (loss)	—	—	—	—	(347,694)	(347,694)
Balance at December 31, 2019	49,272,223	$ 49	$ 1,412,082	$ (2,534)	$ (945,238)	$ 464,359
Issuance of common stock under stock plan	952,205	1	33,282	—	—	33,283
Purchase of common stock under ESPP	38,516	1	2,153	—	—	2,154
Stock-based compensation expense	—	—	76,602	—	—	76,602
Follow on offering, net of issuance costs	6,495,070	6	503,176	—	—	503,182
Issuance of common stock related to collaboration agreement	1,035,519	1	79,305	—	—	79,306
Other comprehensive loss	—	—	—	(2,680)	—	(2,680)
Net income (loss)	—	—	—	—	313,882	313,882
Balance at December 31, 2020	57,793,533	$ 58	$ 2,106,600	$ (5,214)	$ (631,356)	$ 1,470,088
Issuance of common stock under stock plan	1,304,386	1	47,302	—	—	47,303
Purchase of common stock under ESPP	43,167	—	3,313	—	—	3,313
Stock-based compensation expense	—	—	93,035	—	—	93,035
Other comprehensive income	—	—	—	1,081	—	1,081
Net income (loss)	—	—	—	—	(644,085)	(644,085)
Balance at December 31, 2021	59,141,086	$ 59	$ 2,250,250	$ (4,133)	$ (1,275,441)	$ 970,735

The accompanying notes are an integral part of the consolidated financial statements.

Blueprint Medicines Corporation
Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,		
	2021	2020	2019
Cash flows from operating activities			
Net income (loss)	$ (644,085)	$ 313,882	$ (347,694)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Depreciation and amortization	6,479	6,559	5,259
Noncash lease expense	6,306	5,791	4,991
Stock-based compensation	91,630	75,526	54,653
Acquired in-process research and development	259,957	—	—
Accretion of premiums and discounts on investments	1,361	466	(4,949)
Other	3,379	429	—
Changes in assets and liabilities:			
Accounts receivable	(18,143)	(6,387)	(599)
Unbilled accounts receivable	6,338	4,536	(22,597)
Inventory	(12,561)	(6,707)	—
Prepaid expenses and other current assets	4,693	(12,620)	(3,338)
Other assets	(1,786)	1,440	20
Accounts payable	4,221	(791)	1,448
Accrued expenses	6,095	16,214	36,980
Deferred revenue	(4,582)	(4,915)	(94)
Operating lease liabilities	(7,955)	(6,388)	(2,095)
Net cash provided by (used in) operating activities	(298,653)	387,035	(278,015)
Cash flows from investing activities			
Purchases of property and equipment	(3,089)	(3,159)	(14,013)
Purchase of in-process research and development asset, net of cash acquired	(258,152)	—	—
Purchases of investments	(655,449)	(969,437)	(738,387)
Maturities of investments	690,830	538,347	735,934
Net cash used in investing activities	(225,860)	(434,249)	(16,466)
Cash flows from financing activities			
Proceeds from common stock offerings, net of issuance costs	—	503,189	327,466
Net proceeds from stock option exercises and employee stock purchase plan	50,716	35,265	13,288
Proceeds from issuance of common stock related to collaboration agreement	—	79,305	—
Other financing activities	—	—	(116)
Net cash provided by financing activities	50,716	617,759	340,638
Net increase (decrease) in cash, cash equivalents, and restricted cash	(473,797)	570,545	46,157
Cash, cash equivalents and restricted cash at beginning of period	689,804	119,604	73,429
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(888)	(345)	18
Cash, cash equivalents and restricted cash at end of period	$ 215,119	$ 689,804	$ 119,604
Supplemental cash flow information			
Property and equipment purchases unpaid at period end	$ 149	$ 141	$ 958
Cash paid for taxes, net	$ 694	$ 778	$ 185

The accompanying notes are an integral part of the consolidated financial statements.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheets that sum to the total of the same such amounts shown in the consolidated statements of cash flows.

	December 31,		
	2021	2020	2019
Cash and cash equivalents	$ 209,948	$ 684,636	$ 113,938
Restricted cash included in prepaid expenses and other current assets	—	—	500
Restricted cash	5,171	5,168	5,166
Total cash, cash equivalents, and restricted cash shown in consolidated statements of cash flows.	$ 215,119	$ 689,804	$ 119,604

1. Nature of Business

Blueprint Medicines Corporation (the Company), a Delaware corporation incorporated on October 14, 2008, is a precision therapy company focused on genomically defined cancers and blood disorders. The Company's approach is to leverage its novel research engine to systematically and reproducibly identify drivers of diseases in genomically defined patient populations, and to craft highly selective and potent drug candidates that provide significant and durable clinical responses to patients.

The Company has two approved precision therapies and is globally advancing multiple programs for systemic mastocytosis, lung cancer and other genomically defined cancers, and cancer immunotherapy. The Company is devoting substantially all of its efforts to research and development for current and future drug candidates and commercialization of AYVAKIT/AYVAKYT, GAVRETO and any current or future drug candidates that obtain marketing approval.

The Company is subject to a number of risks similar to those of other companies transitioning to a commercial stage, including but not limited to: successful commercialization of its current and future drugs, either by itself or through collaboration with third parties; establishing safety and efficacy in clinical trials and obtaining regulatory approvals for its drug candidates; competition from other companies; compliance with comprehensive and ongoing regulatory requirements and legislative changes; and the need to obtain adequate additional financing to fund the development of its drug candidates. If the Company is unable to raise capital when needed or on attractive terms, it may be forced to delay, reduce, eliminate or out-license certain of its research and development programs or future commercialization efforts.

As of December 31, 2021, the Company had cash, cash equivalents and marketable securities of $1,034.6 million. Based on the Company's current operating plans, the Company anticipates that its existing cash, cash equivalents and marketable securities will be sufficient to enable it to fund its current operations for at least the next twelve months from the issuance of the financial statements.

2. Summary of Significant Accounting Policies and Recent Accounting Pronouncements

Basis of Presentation

The audited consolidated financial statements of the Company included herein have been prepared in accordance with accounting principles generally accepted in the U.S. (GAAP) as found in the Accounting Standards Codification (ASC) and Accounting Standards Update (ASU) of the Financial Accounting Standards Board (FASB) and the rules and regulations of the Securities and Exchange Commission (SEC).

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Blueprint Medicines Security Corporation, which is a Massachusetts subsidiary created to buy, sell and hold securities, Blueprint Medicines (Switzerland) GmbH, Blueprint Medicines (Netherlands) B.V., Blueprint Medicines (UK) Ltd, Blueprint Medicines (Germany) GmbH, Blueprint Medicines (Spain) S.L., Blueprint Medicines (France) SAS, Blueprint Medicines (Italy) S.r.L., and Lengo Therapeutics Inc (Lengo), which was acquired on December 30, 2021. All intercompany transactions and balances have been eliminated.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires the Company's management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and in developing the estimates and assumptions that are used in the preparation of the financial statements. Management must apply significant judgment in this process. Management's estimation process often may yield a range of potentially reasonable estimates and management must select an amount that falls within that range of reasonable estimates. Estimates are used in the following areas, among others: revenue recognition, acquisitions, inventory, operating lease right-of-use assets, operating lease liabilities, stock-based compensation expense, accrued expenses, and income taxes. The length of time and full extent to which the ongoing COVID-19 pandemic will directly

or indirectly impact the Company's business, results of operations and financial condition, including revenues, expenses, reserves and allowances, manufacturing, clinical trials, research and development costs and employee-related amounts, will depend on future developments that are highly uncertain, subject to change and difficult to predict, including as a result of new information that may emerge concerning COVID-19, including the identification and spread of new variants, and the actions taken to contain or treat COVID-19, as well as the economic impact thereof on local, regional, national and international customers and markets. The Company considers the impact of COVID-19 while making the estimates within its consolidated financial statements and there may be changes to those estimates in future periods. Actual results may differ from these estimates.

Significant Accounting Policies

Revenue Recognition

The Company accounts for contracts with customers in accordance with ASC Topic 606, *Revenue from Contracts with Customers* (ASC 606). The Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the Company will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product revenue

The Company generated product revenue from sales of AYVAKIT and GAVRETO in the U.S and sales of AYVAKYT in the European Union to a limited number of specialty distributors and specialty pharmacy providers. These customers subsequently resell the products or dispense the products directly to patients. In addition, the Company entered into arrangements with payors that provide for government mandated rebates, discounts and allowances with respect to the utilization of its products.

Product revenue is recognized when the customer takes control of the product, typically upon delivery to the customer. Product revenue is recorded at the net sales price, or transaction price, which includes estimated reserves for variable consideration resulting from chargebacks, government rebates, trade discounts and allowances, product returns and other incentives that are offered within the contract with customers, healthcare providers, payors and other indirect customers relating to the sales of the Company's product. Reserves are established based on the amounts earned or to be claimed on the related sales. Where appropriate, the Company utilizes the expected value method to determine the appropriate amount for estimates of variable consideration based on factors such as the Company's current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns, the percentage of our products that are sold via these programs, and our product pricing. The amount of variable consideration that is included in the transaction price may be constrained and is included in net product revenues only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from the Company's estimates. If actual results vary from the Company's estimates, the Company adjusts these estimates, which would affect net product revenue and earnings in the period such variances become known.

Chargebacks: Chargebacks for fees and discounts represent the estimated obligations resulting from contractual commitments to sell product to qualified healthcare providers and government agencies at prices lower than the list prices charged to the customers who directly purchase the product from the Company. The customers charge the Company for the difference between what they pay for the product and the ultimate contractually committed or government required lower selling price to the qualified healthcare providers. These reserves are estimated using the

expected value method based upon a range of possible outcomes and are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue.

Government rebates: Government rebates consist of Medicare, Tricare and Medicaid rebates, which were estimated using the expected value method, based upon a range of possible outcomes for the estimated payor mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue. For Medicare, the Company also estimates the number of patients in the prescription drug coverage gap for whom it will owe a rebate under the Medicare Part D program.

Trade discounts and allowances: The Company provides the customers with discounts that are explicitly stated in the contracts and recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, the Company also receives sales order management, inventory management and data services from the customers in exchange for certain fees.

Product returns: The Company estimates the amount of its product sales that may be returned by its customers and records this estimate as a reduction of revenue in the period the related product revenue is recognized. The Company currently estimates product return liabilities using expected value method based on available industry data and its visibility into the inventory remaining in the distribution channel.

Other deductions: Co-pay assistance relates to financial assistance provided to qualified patients, whereby the Company may assist them with prescription drug co-payments required by the patient's insurance provider. Reserves for co-pay assistance are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue.

Collaboration revenue

At contract inception, the Company analyzes its collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, *Collaborative Arrangements* (ASC 808). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606.

For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. The Company evaluates the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. For the co-commercialization and marketing activities of certain of the Company's products and product candidates in a collaboration arrangement, where the Company is the principal on sales transactions with third parties, the Company recognizes revenues, cost of sales and operating expenses on a gross basis in their respective lines in its consolidated statements of operations and comprehensive income (loss). Where the Company is not the principal on sales transactions with third parties, the Company records its share of the revenues, cost of sales and operating expenses on a net basis as revenue (expenses) from the collaboration arrangement in its consolidated statements of operations and comprehensive income (loss).

For elements accounted within scope of ASC 606, to determine the appropriate amount of revenue to be recognized for the arrangements, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must use significant judgment to determine: (a) the performance obligations based on the determination under step (ii) above; (b) the transaction price under step (iii) above; and (c) the stand-alone selling price for each performance obligation identified in the contract for the allocation of transaction price in step (iv) above. The Company uses judgment to determine whether milestones or other variable consideration, except for royalties and

sales-based milestones, should be included in the transaction price as described further below. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied.

Exclusive Licenses. If the license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, are subject to estimates by management and may change over the course of the research and development and licensing agreement. Such a change could have a material impact on the amount of revenue the Company records in future periods.

Research and Development Services. The promises under the Company's collaboration agreements may include research and development services to be performed by the Company on behalf of the partner. Payments or reimbursements resulting from the Company's research and development efforts are recognized as revenue when the services are performed and presented on a gross basis because the Company is the principal for such efforts. Payments or reimbursements from the partner that are the result of a collaborative relationship with the partner, instead of a customer relationship, such as co-development activities, are recorded as a reduction to research and development expense.

Customer Options. If an arrangement is determined to contain customer options that allow the customer to acquire additional goods or services, the goods and services underlying the customer options that are not determined to be material rights are not considered to be performance obligations at the outset of the arrangement, as they are contingent upon option exercise. The Company evaluates the customer options for material rights, or options to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the relative standalone selling price, which is determined based on the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised.

Milestone Payments. At the inception of each arrangement that includes research or development milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant revenue reversal would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties. For arrangements that include sales-based royalties, including milestone payments upon first commercial sales and milestone payments based on a level of sales, which are the result of a customer-vendor relationship and for which the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some

or all of the royalty has been allocated has been satisfied or partially satisfied. To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Consideration received prior to revenue recognition is recorded as deferred revenue in the consolidated balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as current portion of deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion. If the Company transfer goods or services to a customer before the customer pays consideration or before payment is due, the Company records a contract asset as unbilled accounts receivable on the consolidated balance sheets.

For a complete discussion of accounting for collaboration revenues, see Note 11, *Collaboration and License Agreements*.

Accounts Receivable, net

Accounts receivable arise from product sales and amounts due from the Company's collaboration partners. The amount from product sales represents amounts due from specialty distributors and specialty pharmacy providers in the U.S. and in the European Union. The Company monitors economic conditions and the financial performance and credit worthiness of its counterparties to identify facts or circumstances that may indicate that its receivables are at risk of collection. The Company provides reserves against accounts receivable for estimated losses that may result from a customer's inability to pay based on the composition of its accounts receivable, considering past events, current economic conditions, and reasonable and supportable forecasts about the future economic conditions. The contractual life of our accounts receivable is generally short-term. Amounts determined to be uncollectible are charged or written-off against the reserve. For the years ended December 31, 2021 and 2020, the Company did not record any expected credit losses related to outstanding accounts receivable.

Inventory

Inventories are stated at the lower of cost or estimated net realizable value with cost based on the first-in first-out method. Inventory that can be used in either the production of clinical or commercial products is expensed as research and development costs when identified for use in clinical trials. The Company classifies its inventory costs as long-term when it expects to utilize the inventory beyond its normal operating cycle and includes these costs in other assets in the consolidated balance sheets.

Prior to the regulatory approval of its drug candidates, the Company incurs expenses for the manufacture of drug product supplies to support clinical development that could potentially be available to support the commercial launch of those drugs. Until the date at which regulatory approval has been received or is otherwise considered probable, the Company records all such costs as research and development expenses.

The Company performs an assessment of the recoverability of capitalized inventories during each reporting period and writes down any excess and obsolete inventory to its net realizable value in the period in which the impairment is first identified. Such impairment charges, should they occur, are recorded as a component of cost of product sales in the consolidated statements of operations and comprehensive loss. The determination of whether inventory costs will be realizable requires the use of estimates by management. If actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required.

Fair Value Measurements

The Company has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements.

- Level 1 — Fair values are determined utilizing quoted prices (unadjusted) in active markets for identical assets or liabilities that the Company has the ability to access;

- Level 2 — Fair values are determined by utilizing quoted prices for identical or similar assets and liabilities in active markets or other market observable inputs such as interest rates, yield curves and foreign currency spot rates; and

- Level 3 — inputs are unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability. Financial assets and liabilities are classified in their entirety based on the lowest level of input that is significant to the fair value measurement.

The Company's financial assets, which include cash equivalents and marketable securities, have been initially valued at the transaction price, and subsequently revalued at the end of each reporting period, utilizing third-party pricing services. The pricing services utilize industry standard valuation models, including both income and market based approaches, to determine value.

There have been no changes to the valuation methods during the years ended December 31, 2021 and 2020.

Cash and cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less from the date of purchase to be cash equivalents. As of December 31, 2021 and 2020, the Company's cash equivalents comprised of money market funds with less than 90 days from the date of purchase. Cash equivalents are reported at fair value.

Available-for-Sale Investments

The Company classifies marketable debt securities with a remaining maturity when purchased of greater than three months available-for-sale, and marketable debt securities with a remaining maturity date greater than one year as non-current assets. Available-for-sale marketable debt securities are maintained by an investment manager and mainly consist of U.S. treasury securities and U.S. government agency securities. Available-for-sale marketable debt securities are carried at fair value with the unrealized gains and losses included in other comprehensive income (loss) as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the instrument. Realized gains and losses are determined using the specific identification method and are included in other income (expense). The Company reviews its portfolio of available-for-sale debt securities, using both quantitative and qualitative factors, to determine if declines in fair value below cost have resulted from a credit-related loss or other factors. If the decline in fair value is due to credit-related factors, a loss is recognized in net income, whereas if the decline in fair value is not due to credit-related factors, the loss is recorded in other comprehensive income (loss).

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Other comprehensive income (loss) consisted of foreign currency translation adjustments, unrealized gains and losses on available-for-sale investments and unrealized gains and losses on pension benefit obligations.

Research and Development Expenses

Expenditures relating to research and development are expensed in the period incurred. Research and development expenses consist of both internal and external costs associated with the development of the Company's selective cancer therapies and building of its discovery platform. As part of the process of preparing the consolidated financial statements, the Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations or other clinical trial vendors that perform the activities.

In certain circumstances, the Company is required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative

future use for the research and development, until related goods or services are provided. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense.

Selling, General and Administrative Expenses

Selling, general and administrative expenses are primarily comprised of compensation and benefits associated with sales and marketing, finance, human resources, legal, information technology and other administrative personnel, business development, advertising and legal expenses and other general and administrative costs. Advertising costs are expensed as incurred. For years ended December 31, 2021, 2020 and 2019, advertising costs totaled $13.5 million, $9.4 million and $3.3 million, respectively.

Property and Equipment, Net

Property and equipment consists of lab equipment, furniture and fixtures, computer equipment, software, and leasehold improvements, all of which is stated at cost. Expenditures for maintenance and repairs are recorded to expense as incurred, whereas major betterments are capitalized as additions to property and equipment. Depreciation is recognized over the estimated useful lives of the assets using the straight-line method.

Impairment of Long-Lived Assets

The Company continually evaluates whether events or circumstances have occurred that indicate that the estimated remaining useful life of its long-lived assets may warrant revision or that the carrying value of these assets may be impaired. The Company has not recognized any impairment charges associated with long-lived assets for the years ended December 31, 2021, 2020 and 2019.

Leases

Leases are accounted for in accordance with ASC Topic 842, *Leases* (ASC 842). At the inception of a contract, the Company assesses whether the contract is, or contains, a lease. The assessment is based on: (1) whether the contract involves the use of a distinct identified asset, (2) whether the Company obtains the right to substantially all the economic benefit from the use of the asset throughout the period, and (3) whether the Company has the right to direct the use of the asset. At inception of a lease, the Company allocates the consideration in the contract to each lease component based on its relative stand-alone price to determine the lease payments.

Leases are classified as either finance leases or operating leases. A lease is classified as a finance lease if any one of the following criteria are met: the lease transfers ownership of the asset by the end of the lease term, the lease contains an option to purchase the asset that is reasonably certain to be exercised, the lease term is for a major part of the remaining useful life of the asset or the present value of the lease payments equals or exceeds substantially all of the fair value of the asset. A lease is classified as an operating lease if it does not meet any of these criteria.

For all leases at the lease commencement date, a right-of-use asset and a lease liability are recognized. The right-of-use asset represents the right to use the leased asset for the lease term. The lease liability represents the present value of the lease payments under the lease.

The right-of-use asset is initially measured at cost, which primarily comprises the initial amount of the lease liability, plus any initial direct costs incurred if any, less any lease incentives received. All right-of-use assets are reviewed for impairment. The lease liability is initially measured at the present value of the lease payments, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, the secured incremental borrowing rate for the same term as the underlying lease.

Lease payments included in the measurement of the lease liability comprise the following: the fixed noncancelable lease payments, payments for optional renewal periods where it is reasonably certain the renewal period will be exercised, and payments for early termination options unless it is reasonably certain the lease will not be terminated early.

Lease cost for operating leases consists of the lease payments plus any initial direct costs, primarily brokerage commissions, and is recognized on a straight-line basis over the lease term. Included in lease cost are any variable lease

payments incurred in the period that are not included in the initial lease liability and lease payments incurred in the period for any leases with an initial term of 12 months or less. Lease cost for finance leases consists of the amortization of the right-of-use asset on a straight-line basis over the lease term and interest expense determined on an amortized cost basis. The lease payments are allocated between a reduction of the lease liability and interest expense.

The Company has made an accounting policy election to not recognize leases with an initial term of 12 months or less within our consolidated balance sheets and to recognize those lease payments on a straight-line basis in our consolidated statements of income over the lease term.

Stock-Based Compensation Expense

Stock-based compensation awards are accounted for in accordance with ASC Topic 718, *Compensation –Stock Compensation* (ASC 718). The Company expenses the fair value of stock awards granted to employees and members of the board of directors over the requisite service period, which is typically the vesting period. Compensation cost for stock-based awards issued to employees is measured using the estimated fair value at the grant date and is adjusted to reflect actual forfeitures. Fair value of options granted to employees at the date of grant are estimated using the Black-Scholes option-pricing model that requires management to apply judgment and make estimates, including:

- expected volatility, which is calculated based on a blend of the Company's reported volatility data for the length of time that market data is available for the Company's stock and the historical data for a representative group of publicly traded companies, for which historical information is available. For these analyses, the Company selects companies with comparable characteristics to itself including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. Until a sufficient amount of historical information regarding volatility of the Company's own share price became available, the Company computed the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of its stock-based awards;

- risk-free interest rate, which is based on the U.S. Treasury yield curve in effect at the time of grant commensurate with the expected term assumption;

- expected term, which is calculated using the simplified method, as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share-Based Payment,* as the Company has insufficient historical information regarding its stock options to provide a basis for an estimate. Under this approach, the weighted-average expected life is presumed to be the average of the contractual term of ten years and the weighted-average vesting term of the stock options, taking into consideration multiple vesting tranches; and

- dividend yield, which is zero based on the fact that the Company never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

Stock-based awards issued to non-employees, including directors for non-board-related services, are accounted for based on the fair value of such services received or the fair value of the awards granted on the grant date, whichever is more reliably measured. Stock-based awards subject to service-based vesting conditions are expensed on a straight-line basis over the vesting period.

The purchase price of common stock under the Company's 2015 employee stock purchase plan (as amended, the 2015 ESPP) is equal to 85% of the lesser of (i) the fair market value per share of the common stock on the first business day of an offering period and (ii) the fair market value per share of the common stock on the purchase date. The fair value of the discounted purchases made under 2015 ESPP is calculated using the Black-Scholes valuation model. The fair value of the look-back provision plus the 15% discount is recognized as compensation expense over the 180-day purchase period.

Acquisition

When entering an acquisition transaction, the Company first determines whether the transaction is a business combination by applying the definition in ASC Topic 805, *Business Combinations* (ASC 805). The definition of a

"business", requires considerations in the form of two steps: (1) determination of whether "substantially all" of the fair value of the gross assets acquired is concentrated in a single identifiable asset or a group of similar identifiable assets (i.e., "screen test"); if not, then (2) evaluate whether the set of transferred assets and activities meets the definition of a business which includes, at a minimum, an input and a substantive process that together significantly contribute to the ability to create outputs. If the assets acquired are not a business, the Company accounts for the transaction as an asset acquisition. If the transaction is a business combination, it is accounted for by applying the acquisition method.

In asset acquisitions, the Company allocates the cost of a group of assets acquired to the individual assets acquired or liabilities assumed based on their relative fair values. Goodwill is not recognized in an asset acquisition. Any difference between the cost of an asset acquisition and the fair value of the net assets acquired is allocated to the non-monetary identifiable assets based on their relative fair values. The Company follows the guidance in ASC Topic 730 *Research and Development* (ASC 730) and determines whether any acquired research and development assets have alternative use. If they have an alternative future use, they are recognized as assets by the Company. If they have no alternative future use, they are charged to research and development expense at the acquisition date.

In business combinations, the acquisition method is applied, where the identifiable assets acquired, the liabilities assumed, and any noncontrolling interest in the acquiree as well as any goodwill is measured and recognized based on its fair value at acquisition date.

Income Taxes

The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the Company's financial statements or tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position.

Foreign currency translation

The financial statements of each of the Company's subsidiaries with a functional currency other than the U.S. dollar are translated into U.S. dollars using period-end exchange rates for assets and liabilities, historical exchange rates for stockholders' equity and weighted average exchange rates for operating results. Translation gains and losses are included in accumulated other comprehensive income (loss) in stockholders' equity. Foreign currency transaction gains and losses are included in other (expense) income, net in the results of operations.

Concentrations of Credit Risk and Off-Balance-Sheet Risk

The Company has no significant off-balance-sheet risk such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk primarily consist of cash and cash equivalents, investments, accounts receivable and unbilled account receivables.

The Company maintains its cash, cash equivalents and marketable securities in custodian accounts at high quality financial institutions, and as of December 31, 2021 and 2020, substantially all the Company's cash, cash equivalents and marketable securities were invested in money market funds and U.S. government agency securities and treasury obligations, and consequently, the Company believes that such funds are subject to minimal credit risk. The Company has adopted an investment policy that limits the amounts the Company may invest in any one type of investment. The Company has not experienced any credit losses and does not believe it is exposed to any significant credit risk on these funds.

Accounts receivables and unbilled accounts receivables represent amounts arising from product sales and amounts due from the Company's collaboration partners. The Company monitors economic conditions to identify facts or circumstances that may indicate that its receivables are at risk of collection.

Segment and Geographic Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the chief executive officer. The Company and the chief operating decision maker view the Company's operations and manage its business as one operating segment. The Company operates in the U.S. and Europe. All material long-lived assets of the Company reside in the U.S.

New Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies that the Company adopts as of the specified effective date. Unless otherwise discussed below, the Company does not believe that the adoption of recently issued standards have or may have a material impact on its consolidated financial statements and disclosures.

Government assistance

In November 2021, the FASB issued ASU No. 2021-10, *Government Assistance (Topic 832) – Disclosures by Business Entities about Government Assistance* to add annual disclosure requirements related to transactions with a government that are accounted for by applying a grant or contribution accounting model by analogy. The standard is effective for annual periods beginning after December 15, 2021, with early adoption permitted. The Company adopted the new standard on January 1, 2022 and does not expect the adoption of this standard to have a significant impact on the disclosures of its consolidated financial statements.

3. Acquisition

On November 27, 2021, the Company entered into a merger agreement for the acquisition of all the outstanding shares of Lengo Therapeutics Inc. ("Lengo"), a biopharmaceutical company committed to developing novel, best-in-class precision medicines targeting driver mutations in oncology to improve the lives of patients with cancer. The acquisition was completed on December 30, 2021.

Under the terms of the acquisition, the Company agreed to pay Lengo shareholders an upfront consideration of $250.0 million, subject to customary net indebtedness, transaction expenses, and other adjustments, as set forth in the acquisition agreement, and future contingent cash milestone payments of up to $215.0 million, upon achievement of specified regulatory approval and sales milestones. The milestone payments were determined to be contingent consideration which will be recognized when the contingency is resolved, and the consideration is paid or becomes payable.

The total net purchase price was $258.4 million upon closing of the transaction, which consists of the $250.0 million upfront payment, and $8.4 million of adjustments associated with net indebtedness, transaction expenses, and other adjustments per the terms of the agreement.

The acquisition was accounted for as acquisition of assets that did not meet the definition of a business. The asset acquisition did not constitute a business as substantially all of the fair value of the gross assets acquired was concentrated in Lengo's lead compound LNG-451, now known as BLU-451. The acquired assets and liabilities were recorded at their relative fair values and the Company immediately expensed the acquired intellectual property in the consolidated statement of operations and comprehensive loss in the amount of $260.0 million as the acquired assets represent in-process research and development with no alternative future use.

A summary of the net purchase price and the allocation of the consideration is as follows (in thousands):

Purchase price, net of cash acquired	$ 258,377
Identifiable assets and liabilities acquired:	
Net current liabilities	(1,580)
In-process research and development	259,957
Total identifiable net assets acquired	$ 258,377

4. Marketable Securities

Marketable securities consisted of the following at December 31, 2021 and 2020 (in thousands):

December 31, 2021	Amortized Cost	Unrealized Gain	Unrealized Losses	Fair Value
Marketable securities, available-for-sale:				
U.S. government agency securities	$ 498,582	$ 21	$ (1,460)	$ 497,143
U.S. treasury obligations	328,801	—	(1,249)	327,552
Total	$ 827,383	$ 21	$ (2,709)	$ 824,695

December 31, 2020	Amortized Cost	Unrealized Gain	Unrealized Losses	Fair Value
Marketable securities, available-for-sale:				
U.S. government agency securities	$ 746,770	$ 513	$ (14)	$ 747,269
U.S. treasury obligations	117,368	449	—	117,817
Total	$ 864,138	$ 962	$ (14)	$ 865,086

As of December 31, 2021 and 2020, the Company held 74 and 8 securities, respectively, that were in an unrealized loss position. The aggregate fair value of securities held by the Company in an unrealized loss position for less than twelve months as of December 31, 2021 and 2020 were $750.5 million and $125.7 million, respectively, and there were no securities held by the Company in an unrealized loss position for more than twelve months. The Company has the intent and ability to hold such securities until recovery. As a result, the Company did not record any charges for credit-related impairments for its marketable debt securities for the years ended December 31, 2021 and 2020.

As of December 31, 2021, 56 securities with an aggregate fair value of $557.5 million had remaining maturities between one and five years. As of December 31, 2020, 65 securities with an aggregate fair value of $677.9 million had remaining maturities between one and five years.

The Company received proceeds of $690.8 million and $538.3 million from maturities of debt securities for the years ended December 31, 2021 and 2020, respectively. The Company did not realize any gains or losses from maturities of debt securities for the years ended December 31, 2021 and 2020.

5. Fair Value of Financial Instruments

The following table summarizes the Company's cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2021 (in thousands):

Description	December 31, 2021	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 118,880	$ 118,880	$ —	$ —
Marketable securities, available-for-sale:				
U.S. government agency securities	497,143	—	497,143	—
U.S. treasury obligations	327,552	327,552	—	—
Total	$ 943,575	$ 446,432	$ 497,143	$ —

The following table summarizes the Company's cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2020 (in thousands):

Description	December 31, 2020	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 420,567	$ 420,567	$ —	$ —
Marketable securities, available-for-sale:				
U.S. government agency securities	747,269	—	747,269	—
U.S. treasury obligations	117,817	117,817	—	—
Total	$ 1,285,653	$ 538,384	$ 747,269	$ —

6. Product Revenue Reserves and Allowances

In January 2020, the U.S. Food and Drug Administration (FDA) approved AYVAKIT for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. In September 2020, the European Commission granted conditional marketing authorization to AYVAKYT as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation. In June 2021, the FDA granted a subsequent approval for AYVAKIT, expanding the labeled indications to include adult patients with advanced systemic mastocytosis (Advanced SM), including aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN) and mast cell leukemia (MCL).

In September 2020, the FDA granted accelerated approval of GAVRETO for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test. In December 2020, the FDA granted a subsequent accelerated approval for GAVRETO, expanding the labeled indications to include adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, or with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

The Company recorded net product revenue from the U.S. product sales of GAVRETO through June 30, 2021, and on July 1, 2021, the Company transferred certain responsibilities associated with product sales to customers, pricing and distribution matters related to U.S. product sales of GAVRETO to its collaboration partner and did not record any net product revenue from product sales of GAVRETO during the second half of 2021. Products sales of GAVRETO were reflected as part of collaboration loss sharing in the consolidated statements of operations and comprehensive income (loss). For additional information, see Note 11, *Collaboration and License Agreements*.

The following table summarizes revenue recognized from product sales for the years ended December 31, 2021 2020, and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
AYVAKIT/AYVAKYT	$ 52,981	$ 21,262	$ —
GAVRETO	4,706	872	—
Total product revenue	$ 57,687	$ 22,134	$ —

The following table summarizes activity in each of the product revenue allowance and reserve categories for the years ended December 31, 2021 and 2020 (in thousands):

	Year Ended December 31,	
	2021	2020
Beginning balance at January 1	$ 1,192	$ —
Provision related to sales in the current period	8,624	2,515
Adjustment related to prior periods sales	(396)	—
Credits and payments made	(5,075)	(1,323)
Ending balance at December 31	$ 4,345	$ 1,192

The total reserves above, which are included in the Company's consolidated balance sheets as of December 31, 2021 and 2020, are summarized as follows (in thousands):

	As of December 31,	
	2021	2020
Reduction of accounts receivable, net	$ 419	$ 226
Component of accrued expenses	3,926	966
Total revenue-related reserves	$ 4,345	$ 1,192

7. Inventory

Capitalized inventory consists of the following at December 31, 2021 and 2020 (in thousands):

	As of December 31,	
	2021	2020
Raw materials	$ 10,788	$ —
Work in process	17,702	9,488
Finished goods	3,916	914
Total	$ 32,406	$ 10,402

Balance sheet classification

	As of December 31,	
	2021	2020
Inventory	$ 21,817	$ 8,581
Other assets	10,589	1,821
Total	$ 32,406	$ 10,402

Inventory amounts written down as a result of excess, obsolescence, unmarketability or other reasons are charged to cost of sales. For the year ended December 31, 2021, the Company recognized a write-down of $0.6 million. For the year ended December 31, 2020, no write-down was recorded. Long-term inventory, which primarily consists of work in process, is included in other assets in the consolidated balance sheets.

8. Restricted Cash

At December 31, 2021 and 2020, respectively, $5.2 million and $5.2 million, of the Company's cash is restricted by a bank primarily related to security deposits for the lease agreements for the Company's current and former corporate headquarters. For additional information, see Note 16, *Leases*.

9. Property and Equipment, Net

Property and equipment and related accumulated depreciation are as follows (in thousands):

	Estimated Useful Life (Years)	As of December 31, 2021	As of December 31, 2020
Lab equipment	5	$ 13,120	$ 11,418
Furniture and fixtures	4	3,714	3,420
Computer equipment	3	1,714	1,513
Leasehold improvements	Term of lease	36,945	36,946
Software	3	412	412
Construction-in-progress		213	151
Total cost		56,118	53,860
Less: accumulated depreciation and amortization		(25,418)	(19,731)
Total		$ 30,700	$ 34,129

Property, plant and equipment are recorded at historical cost, net of accumulated depreciation. Depreciation expense for the years ended December 31, 2021, 2020 and 2019 was $6.5 million, $6.6 million and $5.3 million, respectively.

10. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31, 2021	As of December 31, 2020
External research and development	$ 68,164	$ 60,255
Employee compensation	29,166	27,622
Accrued professional fees	12,611	10,986
Revenue-related reserves	3,926	966
Other	7,962	6,109
Total	$ 121,829	$ 105,938

11. Collaboration and License Agreements

Zai Lab

On November 8, 2021, the Company entered into a collaboration (the Zai Lab agreement) with Zai Lab (Shanghai) Co., Ltd., (Zai Lab), pursuant to which the Company granted Zai Lab exclusive rights to develop and commercialize the Company's drug candidates BLU-701 and BLU-945 for the treatment of EGFR-driven non-small cell lung cancer in in Greater China, including Mainland China, Hong Kong, Macau and Taiwan (collectively, the Zai Lab territory), either as a monotherapy or as part of a combination therapy. The Company retains exclusive rights to the licensed products outside the Zai Lab territory.

The Company received an upfront cash payment of $25.0 million through December 31, 2021, and subject to the term of Zai Lab agreement, in addition to the upfront payment received, the Company is eligible to receive up to $590.0 million in contingent payments, including specified development, regulatory and sales-based milestones and tiered percentage royalties on a licensed product-by-licensed product basis ranging from the low-teens to mid-teens on annual net sales of each licensed product in the Zai Lab territory, subject to adjustment in specified circumstances. Zai

Lab will be responsible for costs related to clinical trials in the Zai Lab territory, other than the specified shared services costs as defined in the Zai Lab agreement which will be shared by the Company and Zai Lab.

Pursuant to the terms of the Zai Lab agreement, Zai Lab is responsible for conducting all development and commercialization activities in the Zai Lab territory related to the licensed drug candidates. In addition, under the Zai Lab agreement, each party has granted the other party specified intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the Zai Lab agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the Zai Lab agreement.

The Zai Lab agreement will continue on a licensed product-by-product and region-by-region basis until the later of (i) the 12th anniversary of the date of the first commercial sale of a licensed product in the Zai Lab territory, (ii) the date of expiration of the last valid patent claim related to the Company's patent rights of the product in the Zai Lab territory, and (iii) the expiration of the last regulatory exclusivity for that product in a region in the Zai Lab territory. Zai Lab may terminate the agreement for convenience by giving a written notice after the second anniversary of the effective date (a) at least 12 months after the date of notice, in the event such notice is given after the first commercial sale of a licensed product in the Zai Lab territory or (b) at least nine months after the date of such notice, in the event such notice is given prior to the first commercial sale of the first licensed product in the Zai Lab territory. Either party may terminate the Zai Lab agreement for the other party's uncured material breach or insolvency. Upon termination, all licenses and all other rights granted by the Company to Zai Lab will terminate. Each party will retain its joint ownership interests in any joint collaboration technology.

The Company evaluated the Zai Lab agreement to determine whether it is a collaborative arrangement in scope of ASC 808. The Company concluded that the Zai Lab agreement is a collaborative agreement under ASC 808 as both parties are expected to participate in the activities at least through the completion of the clinical trials, both parties will incur significant costs to support the development activities, and the parties will share in the reward. The Company determined that the Zai Lab agreement contained two material components: (i) licenses granted to Zai Lab to exploit and develop each licensed product in the Zai Lab territory and related activities in the Zai Lab territory, including manufacturing, and (ii) the parties' participation in the global development of the licensed products. The Company used the criteria specified in ASC 606 to determine which of the components of the Zai Lab agreement are performance obligations with a customer and concluded that Zai Lab is the Company's customer for the licenses and related activities in the Zai Lab territory under ASC 606. The global development activities under the agreement does not present a transaction with a customer and the payments received by the Company for global development activities, including manufacturing, will be accounted for as a reduction of related expenses.

The Company evaluated the Zai Lab territory specific licenses and related activities under ASC 606 as these transactions are considered transactions with a customer, and identified three material promises at the outset of the Zai Lab agreement, which consists of the following for each licensed product: (1) the exclusive license, (2) the initial know-how transfer and (3) manufacturing activities related to development and commercial supply of the licensed product in the Zai Lab territory . The Company determined that the exclusive license and the initial know-how transfer were not distinct from each other, as the exclusive license has limited value without the corresponding know-how transfer. As such, for the purposes of ASC 606, the Company determined that these two material promises, the exclusive license and the initial know-how, should be combined into one distinct performance obligation. The Company further evaluated the material promise associated with manufacting activities related to development and commercial supply of the licensed products in the Zai Lab territory, given Zai Lab is not obligated to purchase any minimum amount or quantities of the development and commercial supply from the Company, the Company concluded that, for the purpose of ASC 606, the provision of manufacturing activities related to development and commercial supply of the licensed product in Zai Lab territory was an option but not a performance obligation of the Company at the inception of the Zai Lab collaboration agreement and will be accounted for if and when exercised. The Company also concluded that there is no separate material right in connection with the development and commercial supply of the licensed product, as the expected pricing was not issued at a significant and incremental discount. Therefore, the manufacturing activities were excluded as performance obligation at the outset of the arrangement.

The Company evaluated the license under ASC 606 and concluded that the license is a functional intellectual property license. The Company determined that Zai Lab benefited from the license along with the initial know-how transfer at the time of grant, and therefore the related performance obligation is satisfied at a point in time. Additionally, the Company is entitled to sales milestones and royalties from Zai Lab upon future sales of the licensed products in the

Zai Lab territory, and revenue will be recognized when the related sales occur. Costs that are incurred associated with Zai Lab territory specific activities are reimbursable from Zai and will be recognized as revenue.

For the purposes of ASC 606, the transaction price of the Zai Lab agreement as of the outset of the arrangement was determined to be $25.0 million, which consisted of the upfront cash payment. The other potential milestone payments that the Company is eligible to receive were excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The Company satisfied the performance obligation upon delivery of the licenses and initial know-how transfer and recognized the upfront payment of $25.0 million as revenue during the year ended December 31, 2021.

The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and if necessary, the Company will adjust its estimate of the transaction price, and any addition to the transaction price would be recognized as revenue when it becomes probable that inclusion would not lead to a significant revenue reversal.

Roche – Pralsetinib Collaboration

On July 13, 2020, the Company entered into a collaboration agreement (the Roche pralsetinib collaboration agreement) with F. Hoffmann-La Roche Ltd and Genentech, Inc., a member of the Roche Group (collectively, Roche), pursuant to which the Company granted Roche exclusive rights to develop and commercialize the Company's drug candidate pralsetinib worldwide, excluding the CStone territory (as defined below), and a co-exclusive license in the U.S. to develop and commercialize pralsetinib. In addition, Roche has the right to opt in to a next-generation RET compound co-developed by the Company and Roche.

Under the Roche pralsetinib collaboration agreement, the Company received an upfront cash payment of $675.0 million, and through December 31, 2021, the Company has achieved $105.0 million in specified regulatory and commercialization milestones. In addition to upfront and milestone payments received through December 31, 2021, the Company is eligible to receive up to $822.0 million in contingent payments, including specified development, regulatory and sales-based milestones for pralsetinib and any licensed product containing a next-generation RET compound.

In the U.S., the Company and Roche agreed to work together to co-commercialize pralsetinib and equally share responsibilities, profits and losses. In addition, the Company is eligible to receive tiered royalties ranging from high-teens to mid-twenties on annual net sales of pralsetinib outside the U.S., excluding Greater China (the Roche territory). The Company and Roche have also agreed to co-develop pralsetinib globally in RET-altered solid tumors, including non-small cell lung cancer, medullary thyroid carcinoma and other thyroid cancers, as well as other solid tumors. The Company and Roche will share global development costs for pralsetinib at a rate of 45 percent for the Company and 55 percent for Roche up to a specified amount of aggregate joint development costs, after which the Company's share of global development costs for pralsetinib will be reduced by a specified percentage. The Company and Roche will also share specified global development costs for any next-generation RET compound co-developed under the collaboration in a similar manner.

Unless earlier terminated in accordance with its terms, the Roche pralsetinib collaboration agreement will expire on a licensed product-by-licensed product basis (i) in the U.S. upon the expiration of the gross profit sharing term for such licensed product and (ii) outside the U.S. on a country-by-country basis at the end of the applicable royalty term for such licensed product. Roche may terminate the agreement in its entirety or on a licensed product-by-licensed product or country-by-country basis subject to certain notice periods. Either party may terminate the Roche pralsetinib collaboration agreement for the other party's uncured material breach or insolvency. Subject to the terms of the Roche pralsetinib collaboration agreement, effective upon termination of the agreement, the Company is entitled to retain specified licenses to be able to continue to exploit the licensed products.

In connection with the Roche collaboration agreement, on July 13, 2020, the Company also entered into a stock purchase agreement with Roche Holdings, Inc. (Roche Holdings) pursuant to which the Company issued and sold an aggregate of 1,035,519 of shares of common stock to Roche Holdings at a purchase price of $96.57 per share and received $100.0 million in the third quarter of 2020. The closing for a minority portion of the equity investment occurred following the expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and other customary closing conditions.

The Company considered the ASC 606 criteria for combining contracts and determined that the Roche pralsetinib collaboration agreement and stock purchase agreement should be combined into a single contract because they were negotiated and entered into in contemplation of one another. The Company accounted for the common stock issued to Roche Holdings based on the fair market value of the common stock on the dates of issuance. The fair market value of the common stock issued to Roche Holdings was $79.3 million, based on the closing price of the Company's common stock on the dates of issuance, resulting in a $20.7 million premium. The Company determined that the premium paid by Roche Holdings for the common stock should be attributed to the transaction price of the Roche pralsetinib collaboration agreement.

The Company determined that the Roche pralsetinib collaboration agreement contained four material components: (i) licenses granted to Roche to develop and commercialize pralsetinib worldwide, excluding the CStone territory (pralsetinib license); (ii) the Roche territory-specific commercialization activities for pralsetinib, including manufacturing (Roche territory activities); (iii) the parties' joint development activities for pralsetinib worldwide, excluding the CStone territory; and (iv) the parties' joint commercialization activities for pralsetinib in the U.S. The Company considered the guidance in ASC 606 to determine which of the components of the Roche pralsetinib collaboration agreement are performance obligations with a customer and concluded that the pralsetinib license and the Roche territory activities are within the scope of ASC 606 because Roche is the Company's customer in those transactions.

The Company evaluated the Roche pralsetinib license under ASC 606 and concluded that the pralsetinib license is a functional intellectual property license and is a distinct performance obligation. The Company determined that Roche benefited from the pralsetinib license at the time of grant, and therefore the related performance obligation is satisfied at a point in time.

The Company evaluated the Roche territory activities under ASC 606 and identified one material promise associated with manufacturing activities related to development and commercial supply of pralsetinib in the Roche territory for up to 24 months. Given that Roche is not obligated to purchase any minimum amount or quantities of the development and commercial supply from the Company, the Company concluded that, for the purpose of ASC 606, the provision of manufacturing activities related to development and commercial supply of pralsetinib in Roche territory was an option but not a performance obligation of the Company at the inception of the Roche collaboration agreement and will be accounted for if and when exercised. The Company also concluded that there is no separate material right in connection with the development and commercial supply of pralsetinib, as the expected pricing was not issued at a significant and incremental discount. Therefore, the manufacturing activities were excluded as performance obligations at the outset of the arrangement. Additionally, the Company is entitled to sales milestones and royalties from Roche upon future sales of pralsetinib in the Roche territory, and revenue will be recognized when the related sales occur. Costs that are incurred associated with the Roche territory activities are reimbursable from Roche and will be recognized as revenue.

For the purposes of ASC 606, the transaction price of the Roche collaboration agreement as of the outset of the arrangement was determined to be $695.7 million, which consisted of the upfront cash payment of $675.0 million and the $20.7 million premium on the sale of common stock to Roche Holdings, which was allocated to the performance obligation related to the pralsetinib licenses. During the years ended December 31, 2021 and 2020, cash consideration associated with regulatory or commercialization milestones of $50.0 million and $55.0 million respectively, were added to the estimated transaction price of the Roche pralsetinib agreement and recognized revenue in such periods. The other potential milestone payments that the Company is eligible to receive under the Roche pralsetinib agreement have been excluded from the transaction price, as all the remaining milestone amounts were fully constrained based on the probability of achievement. The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and if necessary, the Company will adjust its estimate of the transaction price, and any addition to the transaction price would be recognized as revenue when it becomes probable that inclusion would not lead to a significant revenue reversal.

The following table summarizes revenue recognized under the Roche pralsetinib collaboration during the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Upfront license revenue	$ —	$ 695,694	$ —
License milestone revenue	50,000	55,000	—
Manufacturing and other services related to Roche territory-specific activities	6,022	2,406	—
Total Roche pralsetinib collaboration revenue	$ 56,022	$ 753,100	$ —

For the parties' participation in global development for pralsetinib and the U.S. commercialization activities for GAVRETO, the Company concluded that those activities and cost-sharing payments related to such activities are within the scope of ASC 808, as both parties are active participants in the development, manufacturing and commercialization activities and are exposed to significant risks and rewards of those activities under the Roche pralsetinib collaboration agreement. Payments to or reimbursements from Roche related to the global development activities are accounted for as an increase to or reduction of research and development expenses. Prior to July 1, 2021, the Company was the principal for product sales to customers in the U.S. and recognized revenues on sales to third parties in product revenue, net in its consolidated statements of operations and comprehensive income (loss). On July 1, 2021, Roche took over certain responsibilities associated with product sales to customers, pricing and distribution matters for GAVRETO in the U.S. and became the principal for recording product sales to customers in the U.S., and the Company recognized its portion of the commercial losses sharing as collaboration loss sharing in its consolidated statements of operations and comprehensive income (loss).

The following table summarizes the amount from collaboration loss sharing after Roche became the principal for product sales of GAVRETO to customers in the U.S. (in thousands):

	Year Ended December 31,		
	2021	2020	2019
The Company's share of loss in the U.S. for pralsetinib	$ 7,801	$ —	$ —

The following table summarizes the amounts recognized as reductions to selling, general and administrative expenses related to the commercialization of GAVRETO in the U.S., and reductions to research and development expenses related to global development activities for pralsetinib under the Roche pralsetinib collaboration during the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Reductions to selling, general and administrative expenses	$ 18,753	$ 10,631	$ —
Reductions to research and development expenses	11,192	20,459	—

The following table summarizes the contract assets associated with the Roche pralsetinib collaboration as of December 31, 2021 and 2020 (in thousands):

	December 31, 2021	December 31, 2020
Accounts receivable, net	$ 2,679	$ —
Unbilled accounts receivable	$ 6,802	$ 17,600

Clementia

On October 15, 2019, the Company entered into a license agreement (the Clementia agreement) with Clementia Pharmaceuticals, Inc. (Clementia), a wholly-owned subsidiary of Ipsen S.A. Under the Clementia agreement, the Company granted an exclusive, worldwide, royalty-bearing license to Clementia to develop and commercialize BLU-

782, the Company's oral, highly selective investigational ALK2 inhibitor in clinical development for the treatment of fibrodysplasia ossificans progressive (FOP), as well as specified other compounds related to the BLU-782 program.

Under the Clementia agreement, the Company received an upfront cash payment of $25.0 million and through December 31, 2021, the Company has received $20.0 million cash milestone payments. Subject to the terms of the Clementia agreement, in addition to the upfront and milestone payments received through December 31, 2021, the Company is eligible to receive up to $490.0 million in potential development, regulatory and sales-based milestone payments for licensed products. In addition, Clementia is obligated to pay to the Company royalties on aggregate annual worldwide net sales of licensed products at tiered percentage rates ranging from the low- to mid-teens, subject to adjustment in specified circumstances under the Clementia agreement, and Clementia purchased specified manufacturing inventory from the Company for a total of $1.5 million.

Unless earlier terminated in accordance with the terms of the Clementia agreement, the agreement will expire on a country-by-country, licensed product-by-licensed product basis on the date when no royalty payments are or will become due. Clementia may terminate the agreement at any time on or after the second anniversary of the effective date of the agreement upon at least 12 months' prior written notice to the Company, which cannot be delivered before the first anniversary of the effective date. Either party may terminate the agreement for the other party's uncured material breach or insolvency and in certain other circumstances agreed to by the parties. In certain termination circumstances, the Company is entitled to retain specified licenses to be able to continue to exploit the Clementia licensed products.

The Company evaluated the Clementia agreement under ASC 606 as the agreement represented a transaction with a customer. The Company identified the following material promises under the agreement: (1) the exclusive license to develop, manufacture and commercialize BLU-782; (2) the technology transfer of BLU-782 program; (3) the transfer of existing manufacturing inventory; and (4) the transfer of in-process manufacturing inventory. In addition, the Company determined that the exclusive license and technology transfer were not distinct from each other, as the exclusive license has limited value without the corresponding technology transfer. As such, for the purposes of ASC 606, the Company determined that these four material promises, described above, should be combined into three performance obligations: (1) the exclusive license and the technology transfer; (2) the transfer of existing manufacturing inventory; and (3) the transfer of in-process manufacturing inventory.

The Company determined that the transaction price as of the outset of the arrangement was $46.5 million, which consisted of the upfront amount of $25.0 million, the $20.0 million cash milestone payment due and received in 2020, the purchase of existing manufacturing inventory of $1.2 million and the purchase of in-process manufacturing inventory of $0.3 million. The other potential milestone payments that the Company is eligible to receive were excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The transaction price was allocated to the three performance obligation on a relative stand-alone selling price basis. The Company satisfies the performance obligations upon delivery of the license and completion of the technology transfer and inventory transfers.

During the year ended December 31, 2021 and 2020, no material revenue was recognized from the Clementia collaboration. During the year ended December 31, 2019, the Company recognized $46.2 million as revenue for the delivery of the license, the technology transfer and the transfer of existing manufacturing inventory. There was no revenue deferred as a contract liability associated with the Clementia agreement as of December 31, 2021 and 2020.

CStone Pharmaceuticals

On June 1, 2018, the Company entered into a collaboration and license agreement (the CStone agreement) with CStone Pharmaceuticals (CStone) pursuant to which the Company granted CStone exclusive rights to develop and commercialize the Company's drug candidates avapritinib, pralsetinib and fisogatinib, including back-up forms and certain other forms thereof, in Mainland China, Hong Kong, Macau and Taiwan (each, a CStone region and collectively, the CStone territory), either as a monotherapy or as part of a combination therapy.

The Company received an upfront cash payment of $40.0 million, and through December 31, 2021, the Company has achieved $23.0 million in milestone payments under this collaboration. Subject to the terms of the CStone agreement, in addition to the upfront payments received and milestones achieved through December 31, 2021, the Company will be eligible to receive up to approximately $323.0 million in additional milestone payments, including $95.5 million related to development and regulatory milestones and $227.5 million related to sales-based milestones. In

addition, CStone will be obligated to pay the Company tiered percentage royalties on a licensed product-by-licensed product basis ranging from the mid-teens to low twenties on annual net sales of each licensed product in the CStone territory, subject to adjustment in specified circumstances. CStone will be responsible for costs related to the development of the licensed products in the CStone territory, other than specified costs related to the development of fisogatinib as a combination therapy in the CStone territory that will be shared by the Company and CStone.

Pursuant to the terms of the CStone agreement, CStone is responsible for conducting all development and commercialization activities in the CStone territory related to the licensed products. Subject to specified exceptions, during the term of the CStone agreement, each party has agreed that neither it nor its affiliates will conduct specified development and commercialization activities in the CStone territory related to selective inhibitors of FGFR4, KIT, PDGFRA and RET. In addition, under the CStone agreement, each party has granted the other party specified intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the CStone agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the CStone agreement.

The CStone agreement will continue on a licensed product-by-licensed product and CStone region-by-CStone region basis until the later of (i) 12 years after the first commercial sale of a licensed product in a CStone region in the CStone territory and (ii) the date of expiration of the last valid patent claim related to the Company's patent rights or any joint collaboration patent rights for the licensed product that covers the composition of matter, method of use or method of manufacturing such licensed product in such region. Subject to the terms of the CStone agreement, CStone may terminate the CStone agreement in its entirety or with respect to one or more licensed products for convenience by providing written notice to the Company, and CStone may terminate the CStone agreement with respect to a licensed product for convenience at any time by providing written notice to the Company following the occurrence of specified events. In addition, the Company may terminate the CStone agreement under specified circumstances if CStone or certain other parties challenges the Company's patent rights or any joint collaboration patent rights or if CStone or its affiliates do not conduct any material development or commercialization activities with respect to one or more licensed products for a specified period of time, subject to specified exceptions. Either party may terminate the CStone agreement for the other party's uncured material breach or insolvency. In certain termination circumstances, the parties are entitled to retain specified licenses to be able to continue to exploit the licensed products, and in the event of termination by CStone for the Company's uncured material breach, the Company will be obligated to pay CStone a low single digit percentage royalty on a licensed product-by-licensed product basis on annual net sales of such licensed product in the CStone territory, subject to a cap and other specified exceptions.

The Company evaluated the CStone agreement to determine whether it is a collaborative arrangement for purposes of ASC 808. The Company determined that there were two material components of the CStone agreement: (i) the CStone territory-specific license and related activities in the CStone territory, and (ii) the parties' participation in global development of the licensed products. The Company concluded that the CStone territory-specific license and related activities in the CStone territory are not within the scope of ASC 808 because the Company is not exposed to significant risks and rewards. The Company concluded that CStone is a customer with regard to the component that includes the CStone territory-specific license and related activities in CStone territory, which include manufacturing. For the parties' participation in global development of the licensed products, the Company concluded that the research and development activities and cost-sharing payments related to such activities are within the scope of ASC 808 as both parties are active participants exposed to the risk of the activities under the CStone agreement. The Company concluded that CStone is not a customer with regard to the global development component in the context of the CStone agreement. Therefore, payments received by the Company for global development activities under the CStone agreement, including manufacturing, will be accounted for as a reduction of related expenses.

A summary of manufacturing and research and development services related to the global development activities net of expenses payable to CStone during the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Manufacturing and research and development services related to global development activities, net of expenses payable to CStone	$ 2,358	$ 3,060	$ 3,286

The Company evaluated the CStone territory-specific license and related activities in the CStone territory under ASC 606 as these transactions are considered transactions with a customer. The Company identified the following material promises under the arrangement: (1) the three exclusive licenses granted in the CStone territory to develop, manufacture and commercialize the three licensed products; (2) the initial know-how transfer for each licensed product; (3) manufacturing activities related to development and commercial supply of the licensed products; (4) participation in the joint steering committee (JSC) and joint project teams (JPT); (5) regulatory responsibilities; and (6) manufacturing technology and continuing know-how transfers. The Company determined that each licensed product is distinct from the other licensed products. In addition, the Company determined that the exclusive licenses and initial know-how transfers for each licensed product were not distinct from each other, as each exclusive license has limited value without the corresponding initial know-how transfer. For purposes of ASC 606, the Company determined that participation on the JSC and JPTs, the regulatory responsibilities and the manufacturing technology and continuing know-how transfers are qualitatively and quantitatively immaterial in the context of the CStone agreement and therefore are excluded from performance obligations. As such, the Company determined that these six material promises, described above, should be combined into one performance obligation for each of the three candidates.

The Company evaluated the provision of manufacturing activities related to development and commercial supply of the licensed products as an option for purposes of ASC 606 to determine whether these manufacturing activities provide CStone with any material rights. The Company concluded that the manufacturing activities were not issued at a significant and incremental discount, and therefore do not provide CStone with any material rights. As such, the manufacturing activities are excluded as performance obligations at the outset of the arrangement.

Based on these assessments, the Company identified three distinct performance obligations at the outset of the CStone agreement, which consists of the following for each licensed product: (1) the exclusive license and (2) the initial know-how transfer.

Under the CStone agreement, in order to evaluate the transaction price for purposes of ASC 606, the Company determined that the upfront amount of $40.0 million constituted the entirety of the consideration to be included in the transaction price as of the outset of the arrangement, which was allocated to the three performance obligations. The potential milestone payments that the Company is eligible to receive were excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The Company satisfied the performance obligations upon delivery of the licenses, initial know-how transfers and product trademark and recognized the upfront payment of $40.0 million as revenue during the year ended December 31, 2018.

During the years ended December 31, 2021, 2020, and 2019, cash consideration associated with achieved development milestones of $9.0 million, $2.0 million and $12.0 million, respectively, were added to the estimated transaction price for the CStone agreement and recognized as revenue in such periods. The Company will continue to reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and if necessary, the Company will adjust its estimate of the transaction price, and any addition to the transaction price would be recognized as revenue when it becomes probable that inclusion would not lead to a significant revenue reversal.

During the year ended December 31, 2021, the Company entered into commercial supply agreements and an avapritinib manufacturing technology transfer agreement with CStone related to drug substance of avapritinib and drug product of avapritinib and pralsetinib to assist CStone's commercialization activities conducted specifically for the CStone territory. The manufacturing activities in these agreements were considered as distinct performance obligations from the CStone collaboration agreement and collaboration revenue is recognized upon delivery of the drug substance and drug product to CStone.

A summary of revenue recognized under the CStone agreement during the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
License milestone revenue	$ 9,000	$ 2,000	$ 12,000
Manufacturing services and royalty revenue related to CStone territory-specific activities	24,395	1,630	144
Total CStone collaboration revenue	$ 33,395	$ 3,630	$ 12,144

The following table presents the contract assets associated with the CStone collaboration as of December 31, 2021 and 2020 (in thousands):

	As of December 31,	
	2021	2020
Accounts receivable, net	$ 8,164	$ 563
Unbilled accounts receivable	$ 5,034	$ —

As of December 31, 2021, the Company had $4.8 million of deferred revenue as a contract liability associated with the CStone collaboration. This contract liability mainly resulted from advance payments made by CStone in connection with commercial supply of pralsetinib for the CStone territory. The contract liability associated with the CStone collaboration was $6.5 million at December 31, 2020.

Roche – Immunotherapy Collaboration

In March 2016, the Company entered into a collaboration and license agreement (as amended, the Roche immunotherapy agreement) with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (collectively, Roche) for the discovery, development and commercialization of small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy (including BLU-852, a development candidate for the kinase target MAP4K1, which is believed to play a role in T cell regulation), as single products or possibly in combination with other therapeutics.

Under the Roche immunotherapy agreement, Roche was originally granted up to five option rights to obtain an exclusive license to exploit products derived from the collaboration programs in the field of cancer immunotherapy. Such option rights are triggered upon the achievement of Phase 1 proof-of-concept. As a result of amendments to the Roche immunotherapy agreement in prior periods, the Company and Roche are currently conducting activities for up to two programs under the collaboration. For one of the two collaboration programs, if Roche exercises its option, Roche will receive worldwide, exclusive commercialization rights for the licensed product. For the other collaboration program, if Roche exercises its option, the Company will retain commercialization rights in the U.S. for the licensed product, and Roche will receive commercialization rights outside of the U.S. for the licensed product. The Company will also retain worldwide rights to any products for which Roche elects not to exercise its applicable option.

Prior to Roche's exercise of an option, the Company will have the lead responsibility for drug discovery and preclinical development of all collaboration programs. In addition, the Company will have the lead responsibility for the conduct of all Phase 1 clinical trials other than those Phase 1 clinical trials for any product in combination with Roche's portfolio of therapeutics, for which Roche will have the right to lead the conduct of such Phase 1 clinical trials. Pursuant to the Roche immunotherapy agreement, the parties will share the costs of Phase 1 development for each collaboration program. In addition, Roche will be responsible for post-Phase 1 development costs for each licensed product for which it retains global commercialization rights, and the Company and Roche will share post-Phase 1 development costs for each licensed product for which the Company retains commercialization rights in the U.S.

The Company received an upfront cash payment of $45.0 million in March 2016 upon execution of the Roche immunotherapy agreement, and through December 31, 2021, the Company has achieved $23.5 million in milestone payments under this collaboration. Subject to the terms of the Roche immunotherapy agreement, as amended, in addition to upfront payments received and milestones achieved through December 31, 2021, the Company is eligible to receive up to approximately $319.3 million in contingent option fees and milestone payments related to specified research, preclinical, clinical, regulatory and sales-based milestones. In addition, for any licensed product for which Roche retains worldwide commercialization rights, the Company will be eligible to receive tiered royalties ranging from low double-digits to high-teens on future net sales of the licensed product. For any licensed product for which the Company retains commercialization rights in the U.S., the Company and Roche will be eligible to receive tiered royalties ranging from mid-single-digits to low double-digits on future net sales in the other party's respective territories in which it commercializes the licensed product. The upfront cash payment and any payments for milestones, option fees and royalties are non-refundable, non-creditable and not subject to set-off.

The Roche immunotherapy agreement will continue until the date when no royalty or other payment obligations are or will become due, unless earlier terminated in accordance with the terms of the Roche immunotherapy agreement. Prior to its exercise of its first option, Roche may terminate the Roche immunotherapy agreement at will, in whole or on

a collaboration target-by-collaboration target basis, upon 120 days' prior written notice to the Company. Following its exercise of an option, Roche may terminate the Roche immunotherapy agreement at will, in whole, on a collaboration target-by-collaboration target basis, on a collaboration program-by-collaboration program basis or, if a licensed product has been commercially sold, on a country-by-country basis, (i) upon 120 days' prior written notice if a licensed product has not been commercially sold or (ii) upon 180 days' prior written notice if a licensed product has been commercially sold. Either party may terminate the Roche immunotherapy agreement for the other party's uncured material breach or insolvency and in certain other circumstances agreed to by the parties. In certain termination circumstances, the Company is entitled to retain specified licenses to be able to continue to exploit the licensed products.

The Company assessed this arrangement in accordance with ASC 606 upon the adoption of the new standard on January 1, 2018, and concluded that the contract counterparty, Roche, is a customer prior to the exercise, if any, of an option by Roche. The Company identified the following material promises under the arrangement: (1) a non-transferable, sub-licensable and non-exclusive license to use the Company's intellectual property and collaboration compounds to conduct research activities; (2) research and development activities through Phase 1 clinical trials under the research plan; (3) five option rights for licenses to develop, manufacture, and commercialize the collaboration targets; (4) participation on a joint research committee (JRC) and joint development committee (JDC); and (5) regulatory responsibilities under Phase 1 clinical trials. The Company determined that the license and research and development activities were not distinct from another, as the license has limited value without the performance of the research and development activities. Participation on the JRC and JDC to oversee the research and development activities was determined to be quantitatively and qualitatively immaterial and therefore is excluded from performance obligations. The regulatory responsibilities related to filings and obtaining approvals related to the drugs that may result from each program do not represent separate performance obligations based on their dependence on the research and development efforts. As such, the Company determined that these promises should be combined into a single performance obligation.

The Company evaluated the option rights for licenses to develop, manufacture, and commercialize the collaboration targets to determine whether it provides Roche with any material rights. The Company concluded that the options were not issued at a significant and incremental discount, and therefore do not provide material rights. As such, they are excluded as performance obligations at the outset of the arrangement.

Based on these assessments, the Company identified one performance obligation at the outset of the Roche immunotherapy agreement, which consists of: (1) the non-exclusive license; (2) the research and development activities through Phase 1; and (3) regulatory responsibilities under Phase 1 clinical trials.

Under the Roche immunotherapy agreement, in order to evaluate the appropriate transaction price, the Company determined that as of January 1, 2018, the upfront amount of $45.0 million constituted the entirety of the consideration to be included in the transaction price as of the outset of the arrangement, which was allocated to the single performance obligation. The option exercise payments that may be received are excluded from the transaction price until each customer option is exercised as it was determined that the options are not material rights. The potential milestone payments that the Company is eligible to receive prior to the exercise of the options were initially excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjust its estimate of the transaction price.

Through December 31, 2021, the Company has achieved $23.5 million in milestone payments under this collaboration, and these amounts were added to the estimated transaction price and allocated to the existing performance obligation as it became probable that a significant reversal of cumulative revenue would not occur for each of the research milestones achieved.

The Company recognizes revenue associated with the performance obligation as the research and development services are provided using an input method, according to the costs incurred as related to the research and development activities on each program and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs over this time period and, in management's judgment, is the best measure of progress towards satisfying the performance obligation. The amounts received that have not yet been recognized as revenue are deferred as a contract liability on the Company's consolidated balance sheet and will be recognized over the remaining research and development period until the performance obligation is satisfied.

A summary of revenue recognized under the Roche immunotherapy agreement during the years ended December 31, 2021, 2020 and 2019 is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Roche collaboration research and development services revenue	$ 7,636	$ 14,580	$ 8,165

During the years ended December 31, 2021, 2020 and 2019, the Company recognized the following revenue due to the changes in the contract liability balances (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Amounts included in the contract liability at the beginning of the period	$ 5,080	$ 11,546	$ 4,578

As of December 31, 2021, the Company had revenue deferred as a contract liability related to the Roche immunotherapy agreement of $31.4 million, of which $6.3 million was included in current liabilities, and the research and development services related to the performance obligation are expected to be performed over a remaining period of approximately 3.25 years. As of December 31, 2020, the Company had revenue deferred as a contract liability related to the Roche immunotherapy agreement of $34.7 million, of which $6.1 million was included in current liabilities.

12. Stockholder's Equity

On January 27, 2020, the Company closed a follow-on public offering of 4,710,144 shares of its common stock at a price to the public of $69.00 per share and received net proceeds of $308.4 million, after deducting underwriting discounts and commissions and offering expenses paid by the Company.

On July 30, 2020, the Company entered into the ATM Facility with Cowen, pursuant to which the Company may offer and sell, from time to time at its sole discretion, shares of its common stock having an aggregate offering price of up to $250.0 million through Cowen as sales agent. During the year ended December 31, 2020, the Company issued and sold 1,784,926 shares of its common stock under the ATM Facility and received net proceeds of $194.7 million. The Company did not sell any shares of its common stock under ATM Facility during the year ended December 31, 2021.

13. Stock-based Compensation

2015 Stock Option and Incentive Plan

In 2015, the Company's board of directors and stockholders approved the 2015 Stock Option and Incentive Plan (the 2015 Plan), which replaced the Company's 2011 Stock Option and Grant Plan, as amended (the 2011 Plan). The 2015 Plan includes incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock, restricted stock units, unrestricted stock, performance-based awards and cash-based awards. The Company initially reserved a total of 1,460,084 shares of common stock for the issuance of awards under the 2015 Plan. The 2015 Plan provides that the number of shares reserved and available for issuance under the 2015 Plan will be cumulatively increased on January 1 of each calendar year by 4% of the number of shares of common stock issued and outstanding on the immediately preceding December 31 or such lesser amount as specified by the compensation committee of the board of directors. For the calendar years beginning January 1, 2021 and 2022, the number of shares reserved for issuance under the 2015 Plan was increased by 2,311,741 and 2,365,643 shares, respectively. In addition, the total number of shares reserved for issuance is subject to adjustment in the event of a stock split, stock dividend or other change in the Company's capitalization. As of December 31, 2021, there were 3,027,882 shares available for future grant under the 2015 Plan.

2020 Inducement Plan

In March 2020, the Company's board of directors adopted the 2020 Inducement Plan (the Inducement Plan), pursuant to which the Company may grant, subject to the terms of the Inducement Plan and Nasdaq rules, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units, and other stock-based awards. The Company initially reserved a total of 1,000,000 shares of common stock for the issuance of awards under the Inducement Plan. The number of shares reserved and available for issuance under the Inducement Plan can be increased

at any time with the approval of the Company's board of directors. The Inducement Plan permits the board of directors or a committee thereof to use the stock-based awards available under the Inducement Plan to attract key employees for the growth of the Company. As of December 31, 2021, there were 288,982 shares available for future grant under the Inducement Plan.

Stock-based Compensation Expense

The Company recognized stock-based compensation expense totaling $91.6 million, $75.5 million and $54.7 million for the years ended December 31, 2021, 2020 and 2019, respectively.

Stock-based compensation expense by award type included within the consolidated statements of operations and comprehensive income (loss) is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Stock options	$ 57,912	$ 57,237	$ 47,726
Restricted stock units	33,939	18,407	6,445
Employee stock purchase plan	1,184	958	482
Subtotal	93,035	76,602	54,653
Capitalized stock-based compensation costs	(1,405)	(1,076)	—
Stock-based compensation expense included in total cost and operating expenses	$ 91,630	$ 75,526	$ 54,653

The following table presents stock-based compensation expense that is included in operating expenses by classification within the consolidated statements of operations and comprehensive income (loss) is as follows (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Research and development	$ 39,670	$ 33,642	$ 28,596
Selling, general and administrative	51,960	41,884	26,057
Total stock-based compensation expense included in operating expenses	$ 91,630	$ 75,526	$ 54,653

At December 31, 2021, there was $199.8 million of total unrecognized compensation cost related to non-vested stock awards, which is expected to be recognized over a weighted-average period of 2.6 years.

Stock Options

Stock options granted by the Company generally vest ratably over four years, with a one-year cliff for new employee awards and are exercisable from the date of grant for a period of ten years. The fair value of each option issued to employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Year Ended December 31,		
	2021	2020	2019
Risk-free interest rate	0.96 %	1.02 %	2.21 %
Expected dividend yield	— %	— %	— %
Expected term (years)	6.0	6.0	6.0
Expected stock price volatility	58.03 %	60.48 %	63.83 %

The following table summarizes the stock option activity for the year ended December 31, 2021:

	Shares	Weighted-Average Exercise Price	Remaining Contractual Life (in Years)	Aggregate Intrinsic Value(1) (in thousands)
Outstanding at December 31, 2020	6,030,641	$ 61.28	7.41	$ 306,810
Granted	1,125,514	98.50		
Exercised	(982,791)	48.13		
Canceled	(491,342)	79.27		
Outstanding at December 31, 2021	5,682,022	$ 69.37	6.99	$ 214,675
Exercisable at December 31, 2021	3,499,094	$ 61.30	6.13	$ 160,313

(1) Intrinsic value represents the amount by which the fair market value as of December 31, 2021 of the underlying common stock exceeds the exercise price of the option.

The weighted-average grant date fair value of options granted in the years ended December 31, 2021, 2020 and 2019 was $52.93, $34.77 and $48.96, respectively. The total intrinsic value of options exercised in the years ended December 31, 2021, 2020, and 2019 was $52.3 million, $43.3 million, and $33.8 million, respectively.

At December 31, 2021, the total unrecognized compensation expense related to unvested stock option awards was $93.8 million, which is expected to be recognized over a weighted-average period of approximately 2.4 years.

Restricted stock units

Restricted stock units granted by the Company generally vest ratably over four years. The following table summarizes the restricted stock units activity for the year ended December 31, 2021:

	Shares	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2020	1,171,686	$ 65.37
Granted	999,504	98.62
Vested	(321,645)	66.87
Forfeited	(259,385)	78.31
Unvested shares at December 31, 2021	1,590,160	$ 83.85

The total fair value of restricted stock units vested during the years ended December 31, 2021, 2020 and 2019 was $31.6 million, $7.4 million and $0.7 million, respectively. As of December 31, 2021, the total unrecognized compensation expense related to unvested restricted stock units was $105.9 million, which is expected to be recognized over a weighted-average period of approximately 2.7 years.

2015 Employee Stock Purchase Plan

In 2015, the Company's board of directors and stockholders approved the 2015 ESPP, which became effective upon the closing of the IPO in May 2015. The Company initially reserved a total of 243,347 shares of common stock for issuance under the 2015 ESPP. The 2015 ESPP provides that the number of shares reserved and available for issuance under the 2015 ESPP will be cumulatively increased on January 1 of each calendar years by 1% of the number of shares of common stock issued and outstanding on the immediately preceding December 31 or such lesser amount as specified by the compensation committee of the board of directors. For the calendar years beginning January 1, 2021 and 2022, the number of shares reserved for issuance under the 2015 ESPP was increased by 577,935 and 591,410 shares, respectively. The Company issued 43,167, 38,516, and 20,724 shares under the ESPP during the years ended December 31, 2021, 2020, and 2019 respectively.

14. Net income (loss) per share

Basic net income (loss) per share (earnings per share, EPS) is calculated by dividing net income (loss) by the weighted average shares of common stock outstanding during the period, without consideration for common stock equivalents. Diluted net income (loss) per share is calculated by adjusting weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period. For purposes of the diluted net income (loss) per share calculation, the effect of stock options, unvested restricted stock units and ESPP shares on weighted average number of shares is calculated using the treasury stock method. In periods with reported net operating losses, all common stock equivalents are deemed anti-dilutive such that basic net loss per share and diluted net loss per share are equal.

The calculation of net income (loss) and the number of shares used to compute basic and diluted net income (loss) per share for the years ended December 31, 2021, 2020 and 2019 are as follows (in thousands, except per share data):

	Year Ended December 31,		
	2021	2020	2019
Net income (loss) - basic and diluted	$ (644,085)	$ 313,882	$ (347,694)
Weighted average shares outstanding - basic	58,518	54,534	47,829
Effect of dilutive securities:			
Stock options	—	1,303	—
Restricted stock units	—	331	—
Weighted average shares outstanding - diluted	58,518	56,168	47,829
Net income (loss) per share - basic	$ (11.01)	$ 5.76	$ (7.27)
Net income (loss) per share - diluted	(11.01)	5.59	(7.27)

For the years ended December 31, 2021, 2020 and 2019, the following dilutive securities were not included in the computation of net income (loss) per share because the effect would be anti-dilutive (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Stock options	5,682	4,480	5,796
Restricted stock units	1,590	13	420
ESPP shares	24	19	14
Total	7,296	4,512	6,230

15. Income Taxes

A reconciliation of the U.S. statutory income tax rate to the Company's effective tax rate is as follows for the years ended December 31, 2021, 2020 and 2019:

	Year Ended December 31,		
	2021	2020	2019
Federal income tax (benefit) at statutory rate	21.00 %	21.00 %	21.00 %
Permanent differences	0.07	(0.47)	1.11
In-process research and development	(8.53)	—	—
Federal research and development credits	0.76	(0.96)	0.77
Federal orphan drug credits	4.02	(10.35)	6.90
State income tax, net of federal benefit	1.26	0.08	7.46
Other	(0.05)	1.50	2.13
Foreign rate differential	(0.10)	0.37	(0.03)
Deferred rate change	0.79	2.60	(0.08)
Foreign tax credit	0.39	—	—
Change in valuation allowance	(20.08)	(13.42)	(39.26)
Effective income tax rate	(0.47)%	0.35 %	— %

The Company's deferred tax assets and liabilities consist of the following (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Deferred tax assets:			
Net operating loss carryforwards	$ 243,670	$ 140,769	$ 219,935
Research and development credit carryforwards	36,345	23,679	19,240
Orphan drug credit carryforwards	150,859	125,153	92,538
Accrued expenses and other	40,617	32,206	25,842
Deferred revenue	6,598	7,317	10,971
Deferred lease incentive	—	—	—
Deferred rent	24,798	19,308	26,196
Jublient license	448	—	—
Interest expense	29	—	—
Total gross deferred tax asset	503,364	348,432	394,722
Deferred tax liability			
Depreciation	(5,157)	(5,451)	(4,474)
Right of use assets	(20,059)	(14,539)	(19,869)
UNICAP	(1,966)	—	—
Prepaid expenses	(2)	—	—
Valuation allowance	(476,180)	(328,442)	(370,379)
Net deferred tax asset	$ —	$ —	$ —

Management has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets and has determined that it is more likely than not that the Company will not recognize the benefits of its net federal, foreign and state deferred tax assets, and as a result, a valuation allowance of $476.2 million, $328.4 million and $370.4 million has been established at December 31, 2021, 2020 and 2019, respectively. The change in the valuation allowance was $147.7 million, ($42.0) million and $136.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. The increase of deferred tax asset between December 31, 2021 and 2020 is primarily driven by increased net operating losses (NOL) and credits generated from R&D activities during the year.

The Company has incurred NOL since inception with the exception of year 2020. As of December 31, 2021, the Company had federal and state NOL carryforwards of $872.6 million and $997.1 million, respectively, which begin to expire in 2030, and of which $851.1 million of the Company's federal NOL is post 2017 NOL that will be carried forward indefinitely. As a result of Lengo acquisition (a stock acquisition for tax purposes) in 2021, the Company has a carryover inside tax basis in Lengo's assets and liabilities, including its tax attributes. The Company acquired $66.6 million and $67.1 million of the federal and state NOL carryforwards, respectively, from the acquisition of Lengo. All such acquired NOL is post 2017 NOL and will be carried forward indefinitely for federal purposes. As of December 31, 2021, the Company had federal and state research and development tax credit carryforwards of $19.4 million and $17.7 million, respectively, which begin to expire in 2030. The Company acquired $0.3 million and $0.2 million of the federal and state research development tax credit carryforwards, respectively, from the acquisition of Lengo. As of December 31, 2021, the Company had federal orphan drug credits of $150.9 million, which begin to expire in 2035 and state investment tax credits of $0.6 million, which have begun to expire in 2021. As of December 31, 2021, the Company has foreign tax credits of $2.5 million which will expire in 2031.

The Company has analyzed and validated its research and development tax credits as well as its orphan drug credits for 2011-2020. The Company generated research credits in 2021 but has not conducted a formal study to document its qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards. No amounts are being presented as an uncertain tax position as of December 31, 2021 until such study is completed and the adjustment is known. A valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carry-forwards and the valuation allowance.

The Internal Revenue Code of 1986, as amended (the Code), provides for a limitation of the annual use of NOL and other tax attributes (such as research and development tax credit carryforwards) following certain ownership changes (as defined by the Code) that could limit the Company's ability to utilize these carryforwards. 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. Approximately $2 million of the Company's NOL carryforwards may not be available for utilization within their applicable carryforward periods based on the Section 382 study in 2020. In addition, U.S. tax laws limit the time during which these carryforwards may be applied against future taxes. Therefore, the Company may not be able to take full advantage of these carryforwards for federal or state income tax purposes.

With respect to the net operating losses and research and development tax credit carryforwards acquired from the acquisition of Lengo, the Company has not completed a study to assess whether an ownership change under Section 382 of the Code has occurred, or whether there have been multiple ownership changes since Lengo's formation. Accordingly, the Company's ability to utilize the aforementioned carryforwards may be limited and in turn, may not be able to take full advantage of these carryforwards for federal or state income tax purposes.

Interest and penalty charges, if any, related to unrecognized tax benefits would be classified as income tax expense in the accompanying statements of operations and comprehensive loss. As of December 31, 2021 and 2020, the Company has no unrecognized tax benefits or accrued interest related to unrecognized tax benefits. As of December 31, 2021, the Company was open to examination in the U.S. federal and certain state jurisdictions for all of the Company's tax years since the net operating losses may potentially be utilized in future years to reduce taxable income. Since the Company is in a loss carryforward position, it is generally subject to examination by the U.S. federal, state, and local income tax authorities for all tax years in which a loss carryforward is available.

16. Leases

38 Sidney Street

On February 12, 2015, the Company entered into a lease for approximately 39,000 rentable square feet of office and laboratory space at 38 Sidney Street in Cambridge, Massachusetts, which the initial term of the lease agreement will expire on October 31, 2022. On December 15, 2021, the Company extended the lease term to expire on November 30, 2029, and agreed to pay an initial annual base rent of approximately $4.5 million, which rises annually until it reaches approximately $5.5 million. The lease extension provided the Company with an allowance for leasehold improvements of $0.8 million improvements to be made to the premises. Security deposit of $0.9 million was recorded as restricted cash on the Company's consolidated balance sheet as of December 31, 2021. The Company is subleasing the space to third parties and the term of the subleases will expire on February 28, 2022 and September 30, 2022.

45 Sidney Street

On April 28, 2017, the Company entered into a lease agreement for approximately 99,833 rentable square feet of office and laboratory space located at 45 Sidney Street in Cambridge, Massachusetts. On September 19, 2018, the Company entered into an amendment to the lease agreement to expand the rentable square footage to approximately 139,216 square feet. The initial term of the lease agreement will expire on November 30, 2029, unless terminated sooner. The lease agreement also provides the Company with an option to extend the lease agreement for two consecutive five-year periods at the then fair market annual rent, as defined in the lease agreement.

The Company has agreed to pay for the 99,833 rentable square feet an initial annual base rent of approximately $7.7 million, which increases annually until it reaches approximately $10.6 million in the last year of the initial term. The Company has also agreed to pay an initial annual base rent of approximately $3.2 million for the expansion premises, which increases annually until it reaches approximately $4.2 million in the last year of the initial term for the expansion premises. The amended lease provided the Company with a total tenant improvement allowance of approximately $17.4 million for improvements to be made to the premises. Security deposit of $3.8 million was recorded as restricted cash on the Company's consolidated balance sheet as of December 31, 2021.

The lease agreements do not contain residual value guarantees and the components of lease cost for the years ended December 31, 2021, 2020 and 2019 were as follows (in thousands):

	Year Ended December 31,		
Operating leases:	2021	2020	2019
Lease cost	$ 18,299	$ 17,600	$ 16,162
Sublease income	(2,174)	(2,919)	(2,834)
Net lease cost	$ 16,125	$ 14,681	$ 13,328

The Company has not entered into any material short-term leases or financing leases as of December 31, 2021.

Supplemental cash flow information related to leases for the years ended December 31, 2021 and 2020 was as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Cash paid for amounts included in the measurement of lease liabilities:	$ 14,896	$ 14,444
Lease liabilities arising from obtaining right-of-use assets:		
Operating leases	$ 28,929	$ 479

The weighted average remaining lease term and weighted average discount rate of the operating leases are as follows:

	Operating leases
Weighted average remaining lease term in years	7.8
Weighted average discount rate	7.4%

Future minimum lease payments under non-cancellable leases as of December 31, 2021 were as follows (in thousands):

2022	15,825
2023	17,691
2024	18,183
2025	18,557
2026	19,089
Thereafter	58,912
Total future minimum lease payments	148,257
Less imputed interest	(36,849)
Total	$ 111,408

* Minimum lease payments have not been reduced by minimum net sublease receivables of $2.0 million due in the future under the Company's non-cancelable subleases for the office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts.

17. Employee Benefit Plans

The Company sponsors various retirement and pension plans. The estimates of liabilities and expenses for these plans incorporate a number of assumptions, including expected rates of return on plan assets and interest rates used to discount future benefits.

401(k) Savings Plan

The Company maintains a 401(k) plan for employees (the 401(k) Plan). The 401(k) Plan is intended to qualify under Section 401(k) of the Code, so that contributions to the 401(k) Plan by employees or by the Company, and the

investment earnings on contributions, are not taxable to the employees until withdrawn from the 401(k) Plan, and so that contributions by the Company, if any, will be deductible by the Company when made. Under the 401(k) Plan, employees may elect to reduce their current compensation by up to the statutorily prescribed annual limit and to have the amount of such reduction contributed to the 401(k) Plan. The 401(k) Plan permits the Company to make contributions up to the limits allowed by law on behalf of all eligible employees. The expense related to the 401(k) Plan primarily consists of the Company's matching contributions. The expenses related to the 401(k) Plan for the years ended December 31, 2021, 2020 and 2019 were $3.0 million, $1.9 million and $1.2 million, respectively.

Switzerland Defined Benefit Plan

The Company maintains a pension plan covering employees of its Swiss subsidiary, Blueprint Medicines (Switzerland) GmbH (the "Swiss Plan"). The Swiss Plan is a government-mandated retirement fund that provides employees with a minimum benefit. Employer and employee contributions are made to the Swiss Plan based on various percentages of salary and wages that vary according to employee age and other factors. As is customary with Swiss pension plans, the assets of the Swiss Plan are invested in a collective fund with multiple employers. The Company has no investment authority over the assets of the Swiss Plan, which are held and invested by a Swiss insurance company. The investment strategy of the Swiss Plan is managed by an independent asset manager with the objective of achieving a consistent long-term return which will provide sufficient funding for future pension obligations while limiting risk. As of December 31, 2021, the Swiss Plan had an unfunded status of $3.4 million, which resulted from fair value of plan assets of $4.5 million and projected benefit obligation of $7.9 million. The accumulated benefit obligation at December 31, 2021 was $6.5 million. The Company's net periodic benefit cost for the year ended December 31, 2021 was $2.0 million. The net periodic benefit cost for the years ended December 31, 2020 and 2019 were not material. The contributions to the Swiss Plan for the years ended December 31, 2021, 2020 and 2019 were not material.

18. Commitments and Contingencies

Purchase Commitments Associated with Commercial Supply Agreements

In connection with the commercialization of AYVAKIT/AYVAKYT and GAVRETO, the Company has negotiated manufacturing agreements with certain vendors that require the Company to meet minimum purchase obligations on an annual basis. The aggregate amount of future minimum purchase obligations under these manufacturing agreements over the period of next five years is approximately $34.2 million as of December 31, 2021.

Legal Proceedings

The Company is not currently a party to any material legal proceedings. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of the authoritative guidance that addresses accounting for contingencies. The Company expenses the costs related to its legal proceedings as they are incurred.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, 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 senior management 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. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2021 or 2020.

19. Subsequent Events

During the first quarter of 2022, a $30.0 million development milestone was achieved under our license agreement with Clementia.

Leadership

Kate Haviland
Chief Executive Officer, President, and Board Member

Percy Carter, MBA, Ph.D.
Chief Scientific Officer

Debbie Durso-Bumpus
Chief People Officer

Becker Hewes, M.D.
Chief Medical Officer

Philina Lee, Ph.D.
Chief Commercial Officer

Tracey L. McCain, Esq.
Executive Vice President, Chief Legal and Compliance Officer

Christopher K. Murray, Ph.D.
Executive Vice President, Chief Technical Operations and Quality Officer

Fouad Namouni, M.D.
President, Research and Development

Christina Rossi
Chief Operating Officer

Board of Directors

Jeffrey W. Albers
Chairperson of the Board of Directors, Blueprint Medicines Corporation, Venture Partner, Atlas Ventures

Daniella Beckman
Chief Financial Officer, Tango Therapeutics, Inc.

Alexis Borisy
Executive Chairman and Co-founder, CurieBio, Inc.

Lonnel Coats
Chief Executive Officer, President and Board Member, Lexicon Pharmaceuticals, Inc.

Habib Dable
Part-time Venture Partner, RA Capital Management, L.P.

Mark Goldberg, M.D.
Lecturer in Medicine, Medicine at Harvard Medical School

Nick Lydon, Ph.D., FRS
Co-Founder and Board Member, Recludix Pharma Inc.

Lynn Seely, M.D.
Lead Independent Director, Blueprint Medicines Corporation, President, Chief Executive Officer and Board Member, Lyell Immunopharma, Inc.

John Tsai, M.D.
Former President, Global Drug Development and Chief Medical Officer, Novartis

Annual Meeting of Stockholders

The 2022 annual meeting of stockholders will be held on Wednesday, June 21, 2023 at 3:30 p.m. ET online at http://www.virtualshareholdermeeting.com/BPMC2023

Stock Listing

NASDAQ: BPMC

Independent Auditors

Ernst & Young LLP

SEC Form 10-K

A copy of the Blueprint Medicines' Form-10K filed with the Securities and Exchange Commission is available free of charge from the company's Investor Relations Department by calling (617) 714-6674, emailing ir@blueprintmedicines.com or sending a written request to: Investor Relations, Blueprint Medicines Corporation, 45 Sidney Street, Cambridge, MA 02139

Transfer Agent

The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, 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 Investor Services, P.O. Box 505005, Louisville, KY 40233-5005, or by overnight mail to – Computershare Investor Services, 462 South 4th Street, Suite 1600, Louisville, KY 40202, https://www-us.computershare.com/Investor/#Contact/Enquiry

Cautionary Note Regarding Forward-Looking Statements

This annual report contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, without limitation, statements regarding plans, strategies, timelines and expectations for Blueprint Medicines' current or future approved drugs and drug candidates, including timelines for marketing applications, approvals and launches, the initiation of clinical trials, or the results of ongoing and planned clinical trials and data publications; expectations related to the of the markets for Blueprint Medicines' current or future approved drugs and drug candidates; the potential benefits of any of Blueprint Medicines' current or future approved drugs or drug candidates in treating patients; and Blueprint Medicines' financial performance, strategy, goals and anticipated milestones, business plans and focus. While we believe the forward-looking statements contained in this annual report are accurate, these forward-looking statements represent Blueprint Medicines' beliefs only as of the date of this annual report and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those indicated by such forward-looking statements. 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 and uncertainties related to Blueprint Medicines' ability and plans in continuing to expand a commercial infrastructure, and successfully launching, marketing and selling current or future approved products; Blueprint Medicines' ability to successfully expand the approved indications for AYVAKIT/AYVAKYT or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of Blueprint Medicines' current or future drug candidates; Blueprint Medicines' advancement of multiple early-stage efforts; Blueprint Medicines' ability to successfully demonstrate the safety and efficacy of Blueprint Medicines' drug candidates and gain approval of Blueprint Medicines' drug candidates on a timely basis, if at all; the preclinical and clinical results for Blueprint Medicines' drug candidates, which may not support further development of such drug candidates either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; Blueprint Medicines' ability to obtain, maintain and enforce patent and other intellectual property protection for its products or any drug candidates it is developing; Blueprint Medicines' ability to develop and commercialize companion diagnostic tests for its products or any of its current and future drug candidates; Blueprint Medicines' ability to successfully expand Blueprint Medicines' research platform and the costs thereof; and the success of Blueprint Medicines' current and future collaborations, partnerships or licensing arrangements. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Blueprint Medicines' filings with the Securities and Exchange Commission (SEC), including Blueprint Medicines' Annual Report on Form 10-K for the year ended December 31, 2022, as filed with the SEC on February 16, 2023, and any other filings that we have made or may make with the SEC in the future. Any forward-looking statements contained in this annual report represent Blueprint Medicines' views only as of April 28, 2023 and should not be relied upon as representing its views as of any subsequent date. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

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NASDAQ: **BPMC**