

**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, 2018**

**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**

*(State or other jurisdiction of  
incorporation or organization)*

**45 Sidney Street  
Cambridge, MA**

*(Address of principal executive offices)*

**26-3632015**

*(IRS Employer  
Identification No.)*

**02139**

*(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*

**Common Stock, par value \$0.001 per share**

*Name of Exchange on Which Registered*

**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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

Large accelerated filer

Non-accelerated filer

Accelerated filer

Smaller reporting company

Emerging growth company

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

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

As of June 30, 2018, 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 \$2,785,741,974.

Number of shares of the registrant's common stock, par value \$0.001 per share, outstanding on February 15, 2019: 44,099,429

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive proxy statement for its 2019 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, 2018, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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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.

## 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 “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “seek,” “should,” “target,” “will,” “would” or the negative of these words or other comparable terminology, although not all forward-looking statements contain these identifying words.

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

- the initiation, timing, progress and results of our pre-clinical studies and clinical trials, including our ongoing clinical trials and any planned clinical trials for avapritinib, BLU-667, BLU-554 and BLU-782, and our research and development programs;
- our ability to advance drug candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our drug candidates, if approved;
- the pricing and reimbursement of our drug candidates, if approved;
- the implementation of our business model, strategic plans for our business, drug candidates and technology;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our drug candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of our existing cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. and our collaboration with CStone Pharmaceuticals, as well as our ability to maintain these collaborations and establish other strategic collaborations;
- the development of companion diagnostic tests for our drug candidates;
- our financial performance; and
- developments relating to our competitors and our industry.

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.

## PART I

### Item 1. Business.

#### Overview

We are a precision therapy company focused on genomically defined cancers, rare diseases and cancer immunotherapy. Our approach is to leverage our novel target discovery engine to systematically and reproducibly identify kinases that are drivers of diseases and to craft highly selective and potent drug candidates that may provide significant and durable clinical responses for patients without adequate treatment options. This integrated biology and chemistry approach enables us to identify, characterize and design drug candidates to inhibit novel kinase targets that have been difficult to selectively inhibit. We believe that our uniquely targeted, scalable approach empowers the rapid design and development of new treatments and increases the likelihood of success.

Our most advanced drug candidates are avapritinib, BLU-667, BLU-554 and BLU-782. Our lead drug candidate, avapritinib, is an orally available, potent and highly selective inhibitor that targets KIT and PDGFRA mutations. These mutations abnormally activate receptor tyrosine kinases that are drivers of cancer and proliferative disorders, including gastrointestinal stromal tumors, or GIST, and systemic mastocytosis, or SM. GIST is a rare disease that is a sarcoma, or tumor of bone or connective tissue, of the gastrointestinal tract, or GI tract, and SM is a rare 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 organ dysfunction and failure. We are currently evaluating avapritinib for the treatment of GIST in an ongoing Phase 1 clinical trial in advanced GIST, which we refer to as our NAVIGATOR trial, and an ongoing global, randomized Phase 3 clinical trial comparing avapritinib to regorafenib in third-line GIST, which we refer to as our VOYAGER trial. We have completed enrollment of the NAVIGATOR trial, and we plan to present additional data from this trial in the second quarter of 2019. We expect to complete enrollment of the VOYAGER trial in the second half of 2019. We plan to initiate a Phase 3 precision medicine trial in second-line GIST in the second half of 2019, which we refer to as our COMPASS-2L trial. In addition, we plan to submit a new drug application, or NDA, for avapritinib for the treatment of PDGFRA Exon 18 mutant GIST and fourth-line GIST in the second quarter of 2019, and we plan to submit a supplemental NDA for the treatment of third-line GIST in 2020. We are currently evaluating avapritinib for the treatment of SM in an ongoing Phase 1 clinical trial in advanced SM, which we refer to as our EXPLORER trial, an ongoing registration-enabling Phase 2 clinical trial in advanced SM, which we refer to as our PATHFINDER trial, and an ongoing registration-enabling Phase 2 clinical trial in indolent and smoldering SM, which we refer to as our PIONEER trial. We plan to present updated data from the EXPLORER trial in advanced SM in the second quarter of 2019. We expect to complete the dose-finding portion of the PIONEER trial and plan to present initial data from this trial in indolent and smoldering SM in the second half of 2019. We expect to complete enrollment of the PATHFINDER trial in the second half of 2019. We plan to submit an NDA for advanced SM in 2020. The U.S. Food and Drug Administration, or FDA, has granted orphan drug designation to avapritinib for the treatment of GIST and the treatment of mastocytosis, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of GIST and the treatment of mastocytosis. The FDA has granted fast track designation to avapritinib for (i) the treatment of patients with unresectable or metastatic GIST that progressed following treatment with imatinib and a second TKI and (ii) the treatment of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior therapy. In addition, the FDA has granted breakthrough therapy designation to avapritinib for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation and to avapritinib for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia.

BLU-667 is an orally available, potent and highly selective inhibitor that targets RET, a receptor tyrosine kinase that is abnormally activated by mutations or fusions and RET resistance mutations that we predict will arise from treatment with first generation therapies. RET drives disease in subsets of patients with non-small cell lung cancer, or NSCLC, and cancers of the thyroid, including medullary thyroid carcinoma, or MTC, and papillary thyroid cancer, or PTC, and our research suggests that RET may drive disease in subsets of patients with colon cancer, breast cancer and other cancers. We are currently evaluating BLU-667 in an ongoing Phase 1 clinical trial in patients with RET-altered NSCLC, MTC and other advanced solid tumors, which we refer to as our ARROW trial. We expect to complete enrollment of the previously treated NSCLC and MTC cohorts in the ARROW trial in the second quarter of 2019. In addition, we plan to present updated data from the ongoing ARROW trial in the second quarter of 2019. We plan to submit an NDA for BLU-667 in the first half of 2020 based on additional data from the ongoing ARROW trial and currently expect the NDA submission will be for separate potential indications: (1) patients with RET-fusion positive

NSCLC who have progressed following prior systemic therapy and (2) patients with RET-mutant MTC who have progressed following treatment with a tyrosine kinase inhibitor, or TKI. In addition, in the second half of 2019, we plan to initiate a Phase 3 clinical trial evaluating BLU-667 in first-line RET-altered NSCLC and plan to initiate a Phase 2 clinical trial evaluating BLU-667 in combination with osimertinib in treatment-resistant, EGFR-mutant NSCLC harboring an acquired RET alteration. The FDA has granted orphan drug designation to BLU-667 for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC, and the FDA has granted breakthrough therapy designation to BLU-667 for the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments.

BLU-554 is an 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, the most common type of liver cancer. We are currently evaluating BLU-554 in an ongoing Phase 1 clinical trial in patients with advanced HCC. We and CStone Pharmaceuticals, or CStone, plan to expand our ongoing Phase 1 clinical trial of BLU-554 to include clinical sites in Mainland China by the middle of 2019. In addition, we and CStone plan to initiate a proof-of-concept clinical trial in the second half of 2019 in the CStone territory evaluating BLU-554 in combination with CS1001, a clinical stage anti-programmed death ligand-1 immunotherapy being developed by CStone, as a first-line therapy for the treatment of patients with HCC. The FDA has granted orphan drug designation to BLU-554 for the treatment of HCC.

BLU-782 is an orally available, potent and highly selective inhibitor that targets mutant activin-like kinase 2, or ALK2. We are developing BLU-782 for the treatment of fibrodysplasia ossificans progressiva, or FOP, a rare, severely disabling genetic disease caused by mutations in the ALK2 gene, ACVR1. FOP is characterized by progressive heterotopic ossification, which is the abnormal transformation of muscle, ligaments and tendons into bone. Heterotopic ossification may be spontaneous or associated with painful episodic disease flare-ups that are usually precipitated by soft tissue injury. As the disease progresses, extra-skeletal bone increasingly restricts joints, resulting in severe disability and loss of mobility, compromised respiratory function and increased risk of early death. Currently, there are no approved therapies for FOP. We initiated a Phase 1 clinical trial in healthy volunteers in the first quarter of 2019, and we plan to initiate a Phase 2 clinical trial evaluating BLU-782 in patients with FOP in the first half of 2020. The FDA has granted fast track designation to BLU-782 for the treatment of fibrodysplasia ossificans progressiva.

We also 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. We currently have four wholly-owned discovery programs for undisclosed kinase targets, and we anticipate nominating at least one additional wholly-owned discovery program in 2019.

In addition, we entered into collaborations with F. Hoffmann La Roche Ltd and Hoffmann La Roche Inc., which we collectively refer to as Roche, and CStone in March 2016 and June 2018, respectively. Under our collaboration agreement with Roche, we are seeking to discover, develop and commercialize up to five small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy, as single products or possibly in combination with other therapeutics. Under our collaboration agreement with CStone, we are seeking to develop and commercialize BLU-554, avapritinib and BLU-667, including back-up forms and certain other forms, in Mainland China, Hong Kong, Macau and Taiwan, or the CStone territory, either as a monotherapy or as part of a combination therapy. We will continue to evaluate additional collaborations that could maximize the value for our programs and allow us to leverage the expertise of strategic collaborators. We are also focused on engaging in collaborations to capitalize on our discovery platform outside of our primary strategic focus area of cancer.

We currently have worldwide development and commercialization rights to avapritinib, BLU-667 and BLU-554 other than the rights licensed to CStone in the CStone territory. We currently have worldwide development and commercialization rights to BLU-782 and all of our discovery programs other than the discovery-stage programs under the Roche collaboration.

Despite the success of approved kinase drugs, there is room for further improvement in kinase drug discovery and development. Many of the approved drugs are multi-kinase inhibitors that are not selective for disease drivers. This results in off-target toxicities that limit dose levels and target inhibition, thereby reducing efficacy. Further, patients who initially respond to a targeted kinase treatment often relapse due to the development of resistance mutations. For many of the known kinases, there is a strong link between genomic alterations in a kinase and disease, including specific forms of cancer and rare genetic diseases. However, the function of the majority of the kinome is still unknown, and small molecule drugs approved by the FDA target less than five percent of the 518 kinases. Taken together, this represents a

substantial opportunity for developing novel and transformative drugs for cancer, rare genetic diseases and other disease areas, including cancer immunotherapy.

To capitalize on the kinase opportunity, we built a discovery platform that integrates a novel target discovery engine and a proprietary compound library. Our novel target discovery engine combines our expertise in genomics, bioinformatics, and cell and structural biology to provide new insights into the biology of kinases as drivers of disease. To develop kinase drugs, we start by interrogating our proprietary compound library. Our library is a unique collection of novel small molecules rationally designed and developed entirely in-house by Blueprint Medicines' scientists as kinase inhibitors and enriched for drug-like properties. We do not owe any royalties or other fees to any parties associated with our novel target discovery engine and our proprietary compound library, other than any royalties or other fees that may become payable to Roche under our cancer immunotherapy collaboration. Using this discovery platform, we have produced a drug pipeline of several promising drug candidates that target genomically defined patient subsets.

## Our Strategy

In January 2019, we announced our "2020 Blueprint" strategy, which outlined our strategy to transform Blueprint Medicines into a fully-integrated, global, commercial-stage enterprise focused on delivering a portfolio of precision therapies to patients with cancer and rare diseases. Under this strategy, we anticipate achieving the following by the end of 2020:

- 2 marketed products in the United States and 1 marketed product in Europe;
- 4 additional marketing applications pending in the United States and Europe;
- 6 therapeutic candidates in global clinical development; and
- 8 research programs that leverage strategic areas of focus.

The key tenets of our strategy include the following:

- ***Rapidly advance the clinical development of avapritinib as a potential treatment for broad populations of GIST and SM, and if successful, seek global regulatory approval.***
- ***Rapidly advance the clinical development of BLU-667 as a potential treatment for RET-altered cancers, including RET-altered NSCLC and MTC, and if successful, seek global regulatory approval.***
- ***Prepare for a potential commercial launch of avapritinib and build commercial capability to bring avapritinib and our other drug candidates, if and when approved, to healthcare providers and patients for the approved indications.***
- ***Rapidly advance BLU-554 and BLU-782 through clinical development and define the potential regulatory path for these drug candidates.***
- ***Continue to expand our broad, differentiated pipeline of kinase drug candidates for genomically defined cancers, rare diseases and cancer immunotherapy, with a focus on strategic therapeutic areas where we have scientific and clinical expertise, including GIST, SM and lung cancer.***
- ***Evaluate potential strategic collaborations to maximize the value of our programs and platform.***
- ***Maintain a commitment to Blueprint Medicines' patient-focused and science-driven culture as we grow our business.***

## Our Focus — Highly Selective Kinase Drugs for Genomically Defined Cancers and Rare Diseases

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 genetic diseases. Several kinases have been validated as oncogenes, which are genes that when altered can initiate and maintain cancer growth. Examples of oncogenes are ABL, EGFR, B-RAF, ALK, BTK and JAK, among many others. Ongoing genomic analyses of tumor data sets continue to identify new roles for kinases as drivers of disease.

Despite these successes, many opportunities remain in kinase drug discovery and development.

- **Identifying novel kinase drivers of disease.** Very few kinases are the focus of approved drugs. Further, the function of the majority of the kinome still remains unexplored. Thus, 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, or KUBs, which constitute the majority of the kinome.
- **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.** Most approved kinase inhibitors provide only temporary disease control. Patients may relapse due to the emergence of on-target resistance mutations. Novel approaches are needed to predict and inhibit resistant mutants thus providing more durable clinical responses.

## Our Approach and Platform

Our approach is to systematically and reproducibly identify kinases that are drivers of diseases 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 kinase targets that have been difficult to inhibit selectively and also identify, characterize and design drug candidates to inhibit novel kinase 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.

Our approach is enabled by our drug discovery platform consisting of two pillars:

- a proprietary, highly-annotated library of novel compounds; and

- a novel target discovery engine, which is a comprehensive process that interrogates kinase biology from many angles using genomics, structural biology and cell biology.

Our proprietary compound library is a unique collection of small molecules designed and developed entirely in-house by Blueprint Medicines' scientists as kinase inhibitors and enriched for drug-like properties. We do not owe royalties or other fees to any parties associated with our novel target discovery engine and our proprietary compound library. This provides high-quality compounds to start kinase drug discovery programs and to use in identifying new kinase targets. The compounds were designed as kinase inhibitors without specific targets in mind, a design strategy that yielded a diversity of novel chemical structures that provide access to unique chemical matter. Each compound has been extensively characterized for binding to over 450 kinases and disease-relevant kinase mutants, and the majority of known kinases are targeted by at least one compound family. Thus, this "annotated" compound library provides high-quality medicinal chemistry starting points that enable quick-starts to drug discovery programs, avoiding the expense and time spent running high throughput screens. Notably, our proprietary compound library has yielded high quality chemical starting points for previously difficult-to-drug kinases. We have continued to expand our proprietary compound library to cover a significant portion of the kinome and anticipate that as part of our discovery efforts we will continue to increase the number of compound families that inhibit each kinase target.

We have established a novel target discovery engine, which was developed entirely in-house, to provide new insights into the biology of kinases as drivers of disease and to identify new kinase drug targets. There are two aspects to the novel target discovery engine:

- **Genomics Approach to Identify Novel Kinase Targets.** Our high-capacity computing infrastructure allows not only storage of very large genomic databases but also rapid analyses of these data using proprietary algorithms developed by our bioinformaticians. For example, using our proprietary kinase fusion detection algorithm to analyze human tumor sequences, we have identified both novel kinase fusions and new disease indications for several known kinase fusions. These results were published in *Nature Communications* in 2014.
- **Cell-based Screens to Identify Novel Kinase Targets.** In this approach, a subset of the compounds in our proprietary compound library that exhibit remarkable potency and/or selectivity for one or a few kinases — our "tool compounds" — are used as probes in disease-relevant cell-based screens. Many of these tool compounds inhibit KUBs and thus allow us to evaluate potential roles for these relatively unexplored kinases in human disease.

Another aspect of our novel discovery engine is predicting resistance mutations. Through our structural and cell biology expertise, we predict mutations in kinases that render the enzyme insensitive to inhibition by an approved drug or compound in development. While treatment of patients with genomically defined cancers with a targeted therapy typically results in a significant anti-tumor response, frequently the response is not durable. In tumors driven by an activated kinase, kinase reactivation via mutation is a common mechanism of resistance. Using our structural biology and computational chemistry expertise, we predict what changes in the kinase might result in a resistant enzyme and then confirm this prediction in a relevant cell culture model.

## Our Development Programs

We have leveraged our discovery platform to develop a robust drug pipeline of orally available, potent and selective small molecule kinase inhibitors that target genomic drivers in several cancers and a rare genetic disease. We currently have worldwide development and commercialization rights to avapritinib, BLU-667 and BLU-554 other than the rights licensed to CStone in the CStone territory. We currently have worldwide development and commercialization rights to BLU-782 and all of our discovery programs other than the discovery-stage programs under the Roche collaboration. The following table summarizes our most advanced drug candidates as of February 15, 2019, each of which is described in further detail below.

Drug Candidate (Genomic Target)	Initial Diseases	Stage of Development	Commercial Rights
Avapritinib (KIT and PDGFRA)	PDGFRA Exon 18 mutant GIST <sup>(1)</sup>	Phase 1 enrollment completed (NAVIGATOR) NDA planned for Q2 2019	Blueprint Medicines <sup>(2)</sup>
	Fourth-line GIST <sup>(1)</sup>	Phase 1 enrollment completed (NAVIGATOR) NDA planned for Q2 2019	
	Third-line GIST <sup>(1)</sup>	Phase 1 enrollment completed (NAVIGATOR) Phase 3 ongoing (VOYAGER) NDA planned for 2020	
	Second-line GIST <sup>(1)</sup>	Phase 1 enrollment completed (NAVIGATOR) Phase 3 planned for 2H 2019 (COMPASS-2L)	
	Advanced SM	Phase 1 ongoing (EXPLORER) Phase 2 ongoing (PATHFINDER) NDA planned for 2020	
	Indolent and smoldering SM	Phase 2 ongoing (PIONEER)	
BLU-667 (RET)	Second-line RET-altered NSCLC <sup>(1)</sup>	Phase 1 ongoing (ARROW) NDA planned for 1H 2020	Blueprint Medicines <sup>(2)</sup>
	First-line RET-altered NSCLC <sup>(1)</sup>	Phase 3 planned for 2H 2019	
	Treatment-resistant, EGFR-mutant NSCLC harboring an acquired RET alteration <sup>(1)</sup>	Phase 2 combination with osimertinib planned for 2H 2019	
	Second-line RET-altered MTC <sup>(1)</sup>	Phase 1 ongoing (ARROW) NDA planned for 1H 2020	
	Other advanced RET-altered solid tumors <sup>(1)</sup>	Phase 1 ongoing (ARROW)	
BLU-554 (FGFR4)	Advanced HCC	Phase 1 ongoing	Blueprint Medicines <sup>(2)</sup>
	Advanced HCC	Phase 1 combination with CS1001 planned for 2H 2019	
BLU-782 (ALK2)	FOP	Phase 1 in healthy volunteers ongoing Phase 2 in FOP patients planned for 1H 2020	Blueprint Medicines
Cancer immunotherapy (immunokinase targets)	Oncology	Undisclosed	Blueprint Medicines <sup>(3)</sup> Roche <sup>(4)</sup>

(1) Unresectable or metastatic disease

(2) CStone Pharmaceuticals has exclusive rights to develop and commercialize in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains all rights in the rest of the world.

(3) Blueprint Medicines has U.S. commercialization rights for up to two programs.

(4) Roche has worldwide commercialization rights for up to three programs and ex-U.S. commercialization rights for up to two programs.

All of our current clinical programs target patient populations with genomically defined diseases. Generally, as we advance our drug candidates through Phase 1 clinical development, we enrich our clinical trials by selecting patients most likely to respond to our drug candidates to confirm mechanistic and clinical proof-of-concept. We are also collaborating with third parties to develop and commercialize companion diagnostic tests for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-667 in order to identify NSCLC patients with RET fusions and BLU-554 in order to identify HCC patients with FGFR4 pathway activation. We also plan to collaborate with third parties to develop and commercialize a companion diagnostic test for avapritinib in order to identify GIST patients who do not test positive for the KIT V654A or T670I mutations. We may collaborate with other third parties in the future to develop and commercialize additional companion diagnostic tests or to develop assays to measure target engagement, pathway modulation and early response.

The table below lists the initial diseases and genomic drivers targeted by avapritinib, BLU-667, BLU-554 and BLU-782, and for each of these diseases, the corresponding estimated number of patients in the United States, France, Germany, Italy, Spain, the United Kingdom and Japan, or the Major Markets. In addition, the table lists the estimated frequency of the genomic alterations that we are initially targeting for each of these diseases.

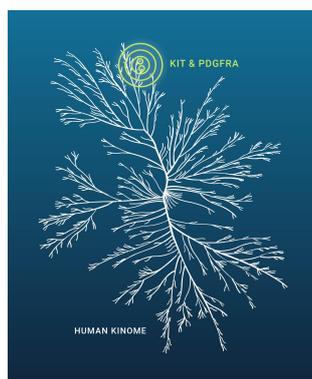
Drug Candidate	Initial Diseases	Estimated Number of Patients <sup>(1)</sup>		Genomic Drivers	Estimated Frequency of Alteration (% of Patients)
		United States	Total Major Markets		
avapritinib	GIST	3,200 first line	8,500 first line	D842V mutant PDGFRA	~5-6% of primary GIST
		2,900 second line	7,500 second line	KIT mutations	~80%
		3,400 ≥ third line	7,400 ≥ third line		
BLU-667	SM	1,100 advanced SM	2,600 advanced SM	KIT D816V mutation	~95%
		700 smoldering SM	1,800 smoldering SM		
		6,700 indolent SM	16,300 indolent SM		
BLU-667	NSCLC	147,300 first line	374,500 first line	RET fusions	~1-2%
		87,800 second line	218,000 second line	RET mutations	~60%
BLU-554	HCC <sup>(2)</sup>	20,200 first line	63,500 first line	Aberrant FGFR4 signaling	~30%
		7,400 second line	22,700 second line		
BLU-782	FOP	400 total	1,100 total	ALK2 mutations	~100%

- (1) Based on estimated prevalence for SM, MTC patients and FOP patients and estimated incidence for GIST, HCC and NSCLC patients. Estimates for GIST, HCC and NSCLC include metastatic and unresectable patient populations.
- (2) The incidence of HCC outside of the Major Markets (including in China, South Korea, Taiwan and Singapore) represents an additional opportunity for BLU-554.

***KIT and PDGFRA Inhibitor Program (avapritinib)***

***Overview***

Avapritinib is an orally available, potent and highly selective inhibitor that targets the homologous kinases KIT and PDGFRA, receptor tyrosine kinases that are drivers of cancer and proliferative disorders when abnormally activated. We specifically designed avapritinib to preferentially interact with the active conformation of KIT and PDGFRA to potently inhibit activation loop mutants not well-targeted by other agents, as well as a broad spectrum of other clinically relevant mutations. Avapritinib is able to potently and selectively inhibit both KIT and PDGFRA mutations with minimal inhibition of other kinases due to the high degree of structural similarity of the kinase domains of KIT and PDGFRA.



Approximate kinome tree locations of KIT and PDGFRA, illustrating close structural similarity between these kinases. Each branch of the dendrogram represents an individual human kinase. *Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc., or CSTI (www.cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.*

We are initially developing avapritinib for PDGFRA-driven GIST and KIT-driven GIST, which we collectively refer to as advanced GIST, and for SM, including advanced SM and indolent and smoldering SM. We also plan to evaluate further development of avapritinib in additional diseases driven by KIT and PDGFRA.

## ***Gastrointestinal Stromal Tumors (GIST)***

### *GIST Disease Background*

GIST is a rare disease that is a sarcoma of the GI tract. Tumors arise within cells in the wall of the GI 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 GI bleeding, incidental findings during surgery or imaging, or in rare cases acute presentation due to tumor rupture or GI 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 15 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.

For patients with KIT-driven GIST, current medical therapies slow the course of disease, but progression is inevitable in most cases. Up to 50% of patients treated with frontline imatinib relapse within approximately 18 months. Of the secondary resistance mutations that lead to relapse, many of the mutations confer resistance to current treatments. A therapy that effectively suppresses a broad spectrum of KIT mutations and that is potentially amenable to combinations with existing agents is needed.

Patients with PDGFRA D842V-driven GIST have great unmet medical need, as no approved medical therapies are effective. Progression can occur within as little as three months, and the median overall survival is 15 months for patients with advanced disease.

### *KIT and PDGFRA Driver Mutations in GIST*

GIST is a tumor type that depends on continued signaling of a single, aberrantly active kinase. Most GISTs result from primary mutations in KIT or PDGFRA. Approximately 80% of patients have KIT-driven GIST. Imatinib effectively inhibits most KIT primary mutations; however over time, secondary mutations occur elsewhere in the KIT gene that lead to kinase activation despite the presence of imatinib, thereby leading to disease progression. The most common mutation in the PDGFRA gene is D842V, found in approximately 5-6% of frontline GIST patients. Currently, there are no therapeutic options for patients with D842V mutant PDGFRA-driven GIST. PDGFRA has a very similar active site structure to KIT, and the PDGFRA D842V mutation is homologous to KIT D816V. As in the case of KIT Exon 17 mutant receptors, the PDGFRA D842V mutation confers ligand-independent constitutive signaling of the mutant PDGFRA kinase.

### ***Avapritinib – Clinical Development for Patients with Advanced GIST***

We are currently evaluating avapritinib for the treatment of GIST in our ongoing Phase 1 NAVIGATOR trial and our ongoing global, randomized Phase 3 VOYAGER trial comparing avapritinib to regorafenib in third-line GIST. In November 2018, we reported updated data from the NAVIGATOR trial at the Connective Tissue Oncology Society, or CTOS, Annual Meeting, and in January 2019, we reported top-line data from the NAVIGATOR trial. We have completed enrollment of the NAVIGATOR trial, and we plan to present additional data from this trial in the second quarter of 2019. We expect to complete enrollment of the VOYAGER trial in the second half of 2019. We plan to initiate our Phase 3 COMPASS-2L trial in second-line GIST in the second half of 2019. In addition, we plan to submit an NDA for avapritinib for the treatment of PDGFRA Exon 18 mutant GIST and fourth-line GIST in the second quarter of 2019, and we plan to submit a supplemental NDA for the treatment of third-line GIST in 2020.

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. In addition, the FDA has granted fast track designation to avapritinib for (i) the treatment of patients with unresectable or metastatic

GIST that progressed following treatment with imatinib and a second TKI and (ii) the treatment of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior therapy. The FDA has granted breakthrough therapy designation to avapritinib for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation.

In August 2016, we entered into an agreement with a third party to develop and commercialize an assay as a companion diagnostic test to identify GIST patients with the PDGFRA D842V mutation for use with avapritinib. We are also working with patient advocacy groups relevant to GIST in order to raise awareness of our ongoing NAVIGATOR and VOYAGER trials; identify and use existing patient registries to identify patients for rapid enrollment; and incorporate the GIST patient perspective into our ongoing activities.

*Phase 1 NAVIGATOR Trial—Top-Line Data Reported in January*

As of the data cutoff date of November 16, 2018, in 43 patients with PDGFRA Exon 18 mutant GIST treated with a starting dose of 300 or 400 mg QD, the objective response rate, or ORR, was 86 percent (one response pending confirmation), and the median duration of response, or DOR, was not reached. As of the data cutoff date, in 111 patients with fourth-line GIST treated with a starting dose of 300 or 400 mg QD, the ORR was 22 percent (one response pending confirmation), and the median DOR was 10.2 months. Top-line safety results were consistent with those previously reported at the CTOS Annual Meeting in November 2018. Avapritinib was well-tolerated, and most adverse events, or AEs, reported by investigators were Grade 1 or 2. Across all doses (n=237), only 23 patients (9.7 percent) discontinued treatment with avapritinib due to treatment-related AEs. These data will form the basis of our planned NDA submission for avapritinib for the treatment of patients with PDGFRA Exon 18 mutant GIST and fourth-line GIST in the second quarter of 2019.

*Phase 1 NAVIGATOR Trial—Data Reported in November 2018 at the CTOS Annual Meeting*

As of the data cutoff date of October 15, 2018, 231 patients were treated with avapritinib in the dose escalation and expansion portions of the NAVIGATOR trial at eight dose levels, ranging from 30 mg QD to 600 mg QD. This population consisted of 167 patients with KIT-driven GIST, 56 patients with PDGFRA D842V-driven GIST and eight patients with other PDGFRA mutations. Patients in the expansion portion of the clinical trial were treated at the recommended Phase 2 dose of 300 mg QD.

*Safety Data.* As of the data cutoff date, avapritinib was well-tolerated, and most AEs reported by investigators were Grade 1 or 2. Across all doses, 20 patients (8.7 percent) discontinued treatment with avapritinib due to treatment-related AEs. Across all grades, the most common treatment-emergent AEs (regardless of relationship to avapritinib) reported by investigators ( $\geq 20$  percent) included nausea (61 percent), fatigue (55 percent), anemia (46 percent), periorbital edema (40 percent), diarrhea (39 percent), vomiting (38 percent), decreased appetite (35 percent), peripheral edema (33 percent), increased lacrimation (31 percent), memory impairment (26 percent), constipation (23 percent), face edema (23 percent), hair color changes (21 percent) and dizziness (20 percent). Investigator-reported Grade 3 or 4 treatment-related AEs ( $\geq 2$  percent) included anemia, fatigue, hypophosphatemia, increased bilirubin, decreased white blood count/neutropenia and diarrhea.

*Clinical Activity Data.* As of the data cutoff date, the following patients were evaluable for response assessments: (i) 56 patients with PDGFRA D842V-driven GIST; (ii) 109 patients with fourth-line or later GIST, (iii) 23 patients with third- or fourth-line GIST who did not receive prior regorafenib (which is comparable to the VOYAGER trial population) and do not harbor the PDGFRA D842V mutation and (iv) 20 patients with second-line GIST who do not harbor the PDGFRA D842V mutation. Patients were evaluable if they had at least one centrally reviewed radiographic scan, and data are based on modified Response Evaluation Criteria in Solid Tumors version 1.1, or mRECIST 1.1 criteria, for GIST.

Across multiple lines of therapy, avapritinib demonstrated important clinical activity in patients with PDGFRA- and KIT-driven GIST.

GIST Population	Evaluable Patients	ORR	Clinical Benefit Rate at Four Months (≥Two Scans)	Median DOR	Median PFS Central Review (Investigator Review)
PDGFRA D842V <sup>a</sup>	56	84% <sup>f</sup>	96%	Not estimable; 76% at 12 months	Not reached
Fourth-line or later <sup>b,c</sup>	109	20% <sup>g</sup>	40%	7.3 months	3.7 months (5.4 months)
Regorafenib-naïve third- or fourth-line <sup>b,d</sup>	23	26%	70%	10.2 months	8.6 months (10.2 months)
Second-line <sup>d,e</sup>	20	25% <sup>h</sup>	NR <sup>i</sup>	NR <sup>i</sup>	NR <sup>i</sup>

Notes: (a) Treated at all doses; (b) Treated at doses of 300 or 400 mg QD; (c) Included patients with the PDGFRA D842V mutation, whose proportion was consistent with the known mutational prevalence in this GIST population; (d) Did not include patients with the PDGFRA D842V mutation, whose proportion was greater than the known mutational prevalence in this GIST population; (e) Treated at doses up to and including 300 or 400 mg QD; (f) Four PR pending confirmation; (g) One PR pending confirmation; (h) Three PR pending confirmation; (i) NR, not reported, as data are too early to estimate.

### Third- and Fourth-Line GIST

Preliminary data showed robust clinical activity in regorafenib-naïve third- and fourth-line GIST patients lacking the PDGFRA D842V mutation. As of the data cutoff date, the ORR was 26 percent, tumor reductions were demonstrated in 78 percent of patients, and the median PFS was 8.6 months per central radiographic review and 10.2 months per investigator review.

In regorafenib-naïve patients with PDGFRA D842V-driven third- or fourth-line GIST, the ORR was 80 percent (eight out of 10 evaluable patients, with one response pending confirmation). Our ongoing Phase 3 VOYAGER trial of avapritinib versus regorafenib in third- or fourth-line GIST permits enrollment of patients with both KIT- and PDGFRA-driven GIST, including patients with the PDGFRA D842V mutation.

### Second-Line GIST

Preliminary data showed a 25 percent ORR in second-line GIST, excluding patients with the PDGFRA D842V mutation. In patients with second-line PDGFRA D842V-driven GIST, the ORR was 94 percent (15 out of 16 evaluable patients, with two responses pending confirmation).

In addition, analyses of circulating tumor DNA, or ctDNA, from the NAVIGATOR trial across all lines showed increased activity for avapritinib in patients without the secondary KIT V654A or T670I mutations, which are estimated to occur in approximately 20 to 25 percent of GIST patients following treatment with imatinib (second-line or later). Independently published data for sunitinib, the current standard of care therapy for second-line GIST, have shown activity against these mutations.

We believe a precision medicine approach has the potential to optimize patient outcomes in second-line GIST and plan to initiate the registration-enabling Phase 3 COMPASS-2L clinical trial in the second half of 2019 using a ctDNA-guided patient selection strategy.

**NAVIGATOR Trial Design.** The NAVIGATOR trial is designed to evaluate the safety and tolerability of avapritinib in patients with advanced GIST. The trial consists of two parts, a dose escalation portion and an expansion portion. The dose escalation portion is complete, and trial objectives include assessing response and measures of pharmacokinetics, or PK, and pharmacodynamics, or PD. Response assessments use blinded, central radiology review. We have completed enrollment of patients in the expansion cohorts of the NAVIGATOR trial and evaluation is ongoing.

### Phase 3 VOYAGER Trial Design

The VOYAGER trial is a global, open-label, randomized, Phase 3 trial designed to evaluate the safety and efficacy of avapritinib versus regorafenib in patients with third- or fourth-line advanced GIST. The trial is designed to enroll approximately 460 patients randomized 1:1 to receive either avapritinib or regorafenib at multiple sites in North America, the European Union, Australia and Asia.

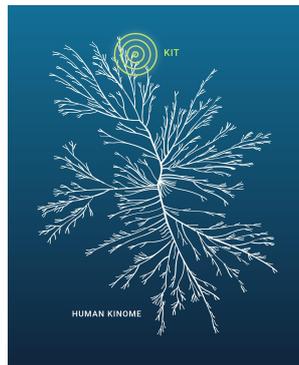
### Phase 3 COMPASS-2L Trial Design

Our planned Phase 3 COMPASS-2L precision medicine trial will evaluate the safety and efficacy of avapritinib versus sunitinib in patients with second-line advanced GIST and pre-specified disease genotypes. The planned trial will select patients with PDGFRA- and KIT-driven second-line GIST who do not test positive for the KIT V654A or T670I mutations and randomize them to receive avapritinib or sunitinib with an anticipated primary endpoint of PFS.

## Systemic Mastocytosis (SM)

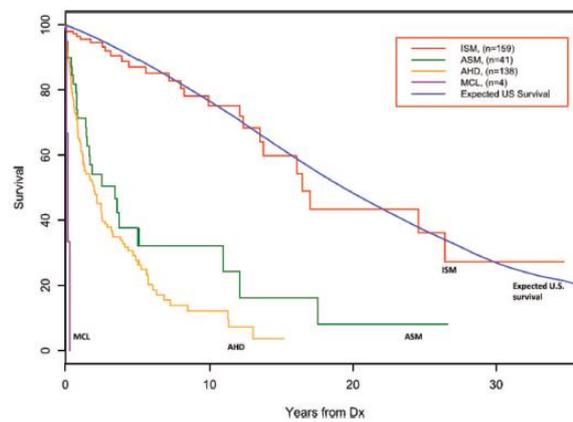
### SM Disease Background

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.



Approximate kinome tree location of KIT. Each branch of the dendrogram represents an individual human kinase. *Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc., or CSTI ([www.cellsignal.com](http://www.cellsignal.com)). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.*

SM comprises a spectrum of disease, with approximately 95% of patients 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 indolent or advanced subtypes of disease, a classification that has prognostic significance as shown below. Patients with ISM have a normal life expectancy. The primary burden of disease for ISM patients is the range of often unpredictable and debilitating allergic symptoms due to mast cell activation. Advanced SM includes three subsets with increasingly severe impact on life expectancy: aggressive SM, or ASM, advanced SM with an associated hematologic neoplasm, SM-AHN, and mast cell leukemia, or MCL. These advanced forms of SM have a median overall survival of three to five years and are characterized by prominent organopathy and dysfunction, as well as symptoms of mast cell activation. Smoldering SM, or SSM, is increasingly considered as a variant of advanced SM. While SSM is not known to affect life expectancy, it has a greater degree of bone marrow infiltration, myeloproliferation and/or presents with an enlarged liver and bears a greater risk of progression to ASM, SM-AHN or MCL.



Overall survival of SM patients. Republished with permission of the American Society of Hematology, from "How I treat patients with indolent and smoldering mastocytosis," A. Pardanani, *Blood*, 121(16):3085 - 3094 (2013); permission conveyed through Copyright Clearance Center, Inc. In the figure above, AHD refers to SM-AHN.

Population studies, including a population-based epidemiology study that we sponsored, based on the Danish National Health Registry, estimate the prevalence of all subtypes of SM from 0.5 to 1/100,000 new patients per year. Of all SM patients, ISM accounts for 50-80% of patients, and advanced SM accounts for the remaining 20-50% of patients.

The current treatment paradigm for SM varies by disease subtype. Currently, there are no approved targeted therapies that address SM patients with the KIT D816V mutation. Midostaurin, which was approved in April 2017 by the FDA for the treatment of advanced SM, is a multi-kinase inhibitor with KIT D816V inhibitory activity and imatinib does not address patients with the KIT D816V mutation. For patients with advanced and smoldering forms of SM, treatments include interferon-alpha or cytoreductive agents to reduce mast cell burden or treatments aimed at addressing the associated blood disorder. Patients with advanced SM typically have a three to five-year overall survival prognosis.

For ISM, management is symptom-directed and includes avoidance of triggers of mast cell activation (such as insect stings). Treatments for ISM include histamine blockers, cromolyn, epinephrine, and, in cases of refractory patients, cytoreductive agents. Within ISM, key opinion leaders see the greatest degree of unmet need for the fraction of patients who have a heavy symptom burden that current therapies fail to address.

#### *KIT D816V Driver Mutation in SM*

In all subtypes of SM, the mast cells of approximately 95% of patients display an activating mutation at the D816V position in KIT. KIT D816V status is routinely assessed as part of the workup in SM diagnosis.

KIT signaling is needed for normal blood cell production, including the differentiation and survival of mast cells. In patients with SM, abnormal mast cells bearing the KIT D816V mutation undergo constitutive kinase activation, leading to continuous survival and proliferative signals. Rare cases of SM have been found where alternative mutations in KIT occur that are responsive to imatinib. In these cases, treatment with imatinib can reduce mast cell burden in the bone marrow and other organs and improve symptoms, thereby clinically validating KIT as a therapeutic target for SM.

#### *Avapritinib – Clinical Development for Patients with SM*

We are currently evaluating avapritinib for the treatment of SM in our ongoing Phase 1 EXPLORER trial in advanced SM, our ongoing registration-enabling Phase 2 PATHFINDER trial in advanced SM and our ongoing registration-enabling Phase 2 PIONEER trial in indolent and smoldering SM. In December 2018, we reported updated data from the EXPLORER trial at the 60<sup>th</sup> American Society of Hematology Annual Meeting and Exposition, or ASH Annual Meeting. We plan to present updated data from the EXPLORER trial in advanced SM in the second quarter of 2019, and we plan to present initial data from the PIONEER trial in indolent and smoldering SM in the second half of 2019. We expect to complete enrollment of the PATHFINDER trial in the second half of 2019. We plan to submit an NDA for advanced SM in 2020.

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. In addition, the FDA has granted breakthrough therapy designation to avapritinib for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia.

*Phase 1 EXPLORER Trial—Data Reported in December 2018 at the ASH Annual Meeting*

As of the data cutoff date of September 30, 2018, 67 patients were treated with avapritinib in the dose escalation and expansion portions of the Phase 1 EXPLORER clinical trial, including 23 patients with aggressive SM, or ASM, 30 patients with advanced SM with an associated hematological neoplasm, or SM-AHN, seven patients with mast cell leukemia, or MCL, and seven patients with indolent or smoldering SM. Forty patients (60 percent) had a prior treatment, including 14 patients (23 percent) who had previously received Rydapt® (midostaurin).

*Safety Data.* As of the data cutoff date, avapritinib was well-tolerated. Most AEs were reported by investigators as Grade 1 or 2. Across all enrolled patients, 52 patients (78 percent) remained on treatment as of the data cutoff date. Three patients (4 percent) discontinued treatment with avapritinib due to treatment-related AEs (refractory ascites, encephalopathy and intracranial bleed). Across all grades, the most common non-hematological treatment-emergent AEs (regardless of relationship to avapritinib) reported by investigators (>15 percent) were periorbital edema, fatigue, nausea, diarrhea, peripheral edema, vomiting, cognitive effects, hair color changes, arthralgia, dizziness and abdominal pain. The most common hematological treatment-emergent AEs reported by investigators (>10 percent) were anemia, thrombocytopenia and neutropenia. Grade 3 and 4 treatment-related AEs occurred in 44 patients (66 percent), and these events were most commonly hematological AEs, typically in patients with low blood counts (cytopenias) at study entry.

*IWG-MRT-ECNM Assessments and Objective Measures of Mast Cell Burden.* As of the data cutoff date, 29 patients were evaluable for response by the modified IWG-MRT-ECNM criteria, a rigorous method for assessing clinical response in advanced SM patients with regulatory precedent in the U.S. and Europe. Responses were centrally reviewed by a committee of SM experts.

Avapritinib demonstrated durable clinical responses across all doses studied and in each subtype of advanced SM – ASM, SM-AHN and MCL. The duration of treatment was up to 31 months as of the data cutoff date, with a median follow-up time of 14 months in evaluable patients.

Across all evaluable patients at all doses, the ORR was 83 percent. Seven patients had a CR/CRh (24 percent, two pending confirmation), 14 patients had a partial response, or PR (48 percent, three pending confirmation), and three patients had clinical improvement, or CI (10 percent, one pending confirmation). Three of the pending responses were previously confirmed responses, or CR (two PRs, one clinical CI), that were transitioning to a deeper response. No patients had documented disease progression per modified IWG-MRT-ECNM criteria.

In addition, strong clinical activity was demonstrated in evaluable patients treated with a starting dose of less than or equal to 200 mg QD, the dose under evaluation in the ongoing registration-enabling Phase 2 PATHFINDER clinical trial in patients with advanced SM. These 10 patients had an ORR of 90 percent and a CR/CRh rate of 50 percent (one CR pending confirmation).

All patients evaluable on objective measures of mast cell burden showed reductions from baseline. These results were shown regardless of disease subtype, prior therapy (including midostaurin or the investigational agent DCC-2618) or co-mutation status. These measures consisted of declines in bone marrow mast cells, serum tryptase, spleen volume and KIT D816V mutant allele burden.

At baseline, 22 SM patients received steroids for mastocytosis symptoms. As of the data cutoff date, 18 patients (80 percent) decreased their steroid dose, including nine patients (41 percent) who were able to entirely discontinue their steroids.

*Patient-Reported Outcomes.* As of the data cutoff date, 32 patients in the dose expansion portion of the Phase 1 EXPLORER trial were evaluated using the AdvSM-SAF, the first patient-reported outcomes tool developed specifically for advanced SM patients. It was designed to evaluate symptoms across the gastrointestinal domain (abdominal pain,

diarrhea, nausea and vomiting) and skin domain (spots, itching and flushing), as well as fatigue. Patients reported their symptoms daily using an electronic diary.

In advanced SM patients, benefits were shown across each individual symptom studied. There was a 41 percent improvement from baseline in the AdvSM-SAF Total Symptom Score ( $p=0.043$ ). The most symptomatic patients ( $n=16$ , top 50<sup>th</sup> percentile) had the largest mean improvement in the AdvSM-SAF Total Symptom Score (46 percent,  $p=0.038$ ).

In addition, an improvement in patient-reported quality of life was observed. As of the data cutoff date, 30 patients were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, a validated and commonly used patient-reported outcomes tool in oncology clinical trials. Results showed a statistically significant improvement in quality of life score, approaching levels observed in healthy aged-matched controls, with a pronounced improvement observed in the most symptomatic patients.

*Proof-of-Concept in Indolent and Smoldering SM.* All evaluable patients with indolent and smoldering SM showed profound reductions in bone marrow mast cells, serum tryptase, spleen volume and KIT D816V mutant allele burden. The data also showed avapritinib led to improvements in patient-reported symptoms. These encouraging data support ongoing Phase 2 PIONEER clinical trial in patients with indolent and smoldering SM.

*EXPLORER Trial Design.* The EXPLORER trial is designed to identify the recommended Phase 2 dose for avapritinib for further study and demonstrate proof-of-concept in advanced SM. The dose escalation portion is complete, and the expansion portion of the trial is enrolling patients with ASM, SM-AHN and MCL. Trial objectives include assessing safety and tolerability, response per modified IWG-MRT-ECNM criteria and patient-reported outcomes. The expansion cohorts of the EXPLORER trial are designed to enroll approximately 55 patients at multiple sites in the United States and European Union.

#### *Phase 2 PATHFINDER Trial Design*

The ongoing Phase 2 PATHFINDER clinical trial is an open-label, single-arm, registration-enabling clinical trial in patients with advanced SM, which is designed to enroll approximately 60 patients at multiple sites in the United States, Canada and European Union. In the PATHFINDER trial, patients will be treated with avapritinib at a dose of 200 mg QD. The primary efficacy endpoints are ORR and DOR based on modified IWG-MRT-ECNM criteria.

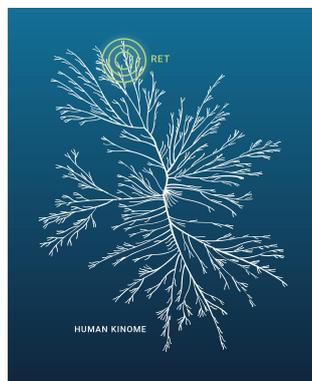
#### *Phase 2 PIONEER Trial Design*

The Phase 2 PIONEER clinical trial is a randomized, placebo-controlled, registration-enabling trial in patients with indolent and smoldering SM. The primary endpoint will be symptom reductions for avapritinib versus placebo based on the Indolent and Smoldering SM Assessment Form Total Symptom Score. The PIONEER trial will be conducted in three parts: a dose-finding portion (part 1); a placebo-controlled efficacy portion (part 2); and an open-label extension portion (part 3). Three doses will be evaluated during part 1: 25 mg QD, 50 mg QD and 100 mg QD. All patients who complete part 2 will have the opportunity to participate in part 3 and receive avapritinib. The PIONEER trial is designed to enroll approximately 224 patients across all three parts at multiple sites in the United States, Canada and European Union.

### **RET Program**

#### *Overview*

BLU-667 is an orally available, potent selective inhibitor of the kinase RET, including activating RET fusions and mutations and predicted RET resistance mutations. 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 MTC (approximately 60% of patients), and RET fusions are implicated in several cancers, including papillary thyroid carcinoma (approximately 10% of patients) and NSCLC (1-2% of patients). Our genomics analyses on the landscape of kinase fusions, published in *Nature Communications* in 2014, identified RET fusions in breast and colon cancer patient samples (both <1% of patients), providing a therapeutic rationale for the use of RET inhibitors in multiple patient subpopulations.



Approximate kinome tree location of RET. Each branch of the dendrogram represents an individual human kinase. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc., or CSTI ([www.cellsignal.com](http://www.cellsignal.com)). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

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 and duration of response 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.

#### *BLU-667 Pre-Clinical Development in RET*

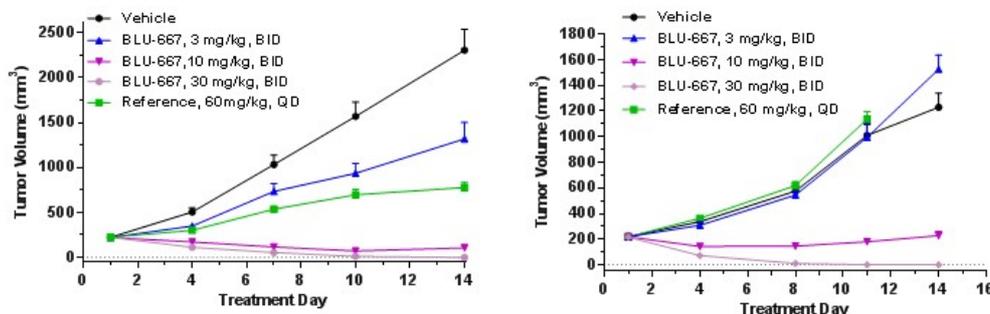
BLU-667 was specifically designed to target oncogenic RET fusions and activating mutations and predicted RET resistance mutations, while sparing anti-targets such as VEGFR-2. We have conducted pre-clinical experiments in biochemical and cellular assays to characterize the potency of BLU-667 against these targets. In a panel comparing BLU-667 with the commonly used multi-kinase inhibitors cabozantinib and vandetanib and the development candidate RXDX-105, BLU-667 was the only compound to demonstrate sub-nanomolar selectivity for wild-type RET and predicted resistance mutations at the gatekeeper (V804) residue. In addition, BLU-667 selectivity was assessed in a biochemical screen of a broad panel of over 350 kinases and demonstrated approximately 90-fold selectivity for wild-type RET over VEGFR-2.

	Biochemical IC <sub>50</sub> (nM)						IC <sub>50</sub> Ratio (VEGFR-2 / RET)
	Wild-type RET	RET V804L	RET V804M	RET M918T	CCDC6- RET	VEGFR- 2	
BLU-667	0.4	0.3	0.4	0.4	0.4	35	88x
cabozantinib	11	45	162	8	34	2	0.2x
vandetanib	4	3597	726	7	20	4	1x
RXDX-105	3	188	102	4	7	17	6x

Potency of BLU-667 against wild-type RET, predicted RET resistant mutants and the anti-target VEGFR-2 compared to a panel of multi-kinase inhibitors with RET inhibitory activity. The inhibitory potencies of BLU-667 and the multi-kinase inhibitors against wild-type

RET, RET resistant mutants and VEGFR2 were evaluated in *in vitro* enzyme activity assays. The inhibitory potencies of these compounds were also evaluated in cell lines driven by either a wild-type RET fusion or a mutant RET fusion.

We have demonstrated significant anti-tumor efficacy with BLU-667 in both a KIF5b-RET fusion allograft and a KIF5b-RET (V804L) resistant mutant allograft. Administration of BLU-667 orally twice daily for 14 days in a wild-type RET fusion allograft and for 14 days in a predicted RET resistant mutant allograft resulted in robust and dose-dependent tumor growth inhibition. At a dose of 30 mg/kg twice daily, a well-tolerated dose, the compound induced tumor regression in both models. The anti-tumor efficacy of a multi-kinase inhibitor with RET inhibitory activity that is being evaluated in the clinic for treatment of patients with RET fusion positive lung cancer (reference compound) was also evaluated in these models. This reference compound, dosed orally once daily at 60 mg/kg, a well-tolerated dose, inhibited tumor growth in the wild-type RET fusion allograft. At the same dose level in the RET resistant mutant allograft, this reference compound showed diminished inhibition of tumor growth.



BLU-667, a RET inhibitor, elicits dose dependent tumor growth inhibition in both a KIF5b-RET fusion allograft (left figure) and a KIF5b-RET (V804L) resistant mutant allograft model (right figure). In the figure above, BID means twice a day, and QD means once a day.

### **BLU-667 – Clinical Development for Patients with RET-Altered NSCLC, MTC and Other Advanced Solid Tumors**

BLU-667 is an orally available, potent and highly selective inhibitor that targets RET, a receptor tyrosine kinase that is abnormally activated by mutations or fusions, and RET resistance mutations that we predict will arise from treatment with first generation therapies. RET drives disease in subsets of patients with NSCLC and cancers of the thyroid, including MTC and PTC. Our research suggests that RET may also drive disease in subsets of patients with colon cancer, breast cancer and other cancers. We are currently evaluating BLU-667 in our ongoing Phase 1 ARROW trial in patients with RET-altered NSCLC, MTC and other advanced solid tumors. In April 2018, we presented initial data from the ongoing ARROW trial at the American Association for Cancer Research, or AACR Annual Meeting, and in October 2018, we presented updated data from the ongoing ARROW trial in RET-altered MTC and PTC at the 88<sup>th</sup> Annual Meeting of the American Thyroid Association, or ATA Annual Meeting. In addition, in September 2018, we presented two clinical cases demonstrating proof-of-concept for BLU-667 in combination with osimertinib (Tagrisso®) in treatment-resistant, EGFR-mutant NSCLC at the International Association for the Study of Lung Cancer 19<sup>th</sup> World Conference on Lung Cancer, or World Lung Conference, and published online in *Cancer Discovery*.

We expect to complete enrollment of the previously treated NSCLC and MTC cohorts in the ARROW trial in the second quarter of 2019. In addition, we plan to present updated data from the ongoing ARROW trial in the second quarter of 2019. We plan to submit an NDA for BLU-667 in the first half of 2020 based on additional data from the ongoing ARROW trial and currently expect the NDA submission will be for separate potential indications: (1) patients with RET-fusion positive NSCLC who have progressed following prior systemic therapy and (2) patients with RET-mutant MTC who have progressed following treatment with a tyrosine kinase inhibitor, or TKI. In addition, in the second half of 2019, we plan to initiate a Phase 3 clinical trial evaluating BLU-667 in first-line RET-altered NSCLC and plan to initiate a Phase 2 clinical trial evaluating BLU-667 in combination with osimertinib in treatment-resistant, EGFR-mutant NSCLC harboring an acquired RET alteration.

The FDA has granted orphan drug designation to BLU-667 for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC, and the FDA has granted breakthrough therapy designation to BLU-667 for the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments.

*Phase 1 ARROW Trial—Data Reported in April 2018 at the AACR Annual Meeting*

As of the data cutoff date of April 6, 2018, 53 patients had been treated with BLU-667 in the dose escalation portion of the Phase 1 ARROW trial across multiple dose levels ranging from 30 mg to 600 mg QD, including 19 patients with NSCLC, 29 patients with MTC and five patients with other solid tumors. Of these 53 patients, 27 patients (51 percent) had been previously treated with a multi-kinase inhibitor and 18 patients (34 percent) had been previously treated with an immunotherapy. PK data across all QD dose levels demonstrated rapid absorption of BLU-667 and a mean half-life greater than 12 hours, supporting a QD dosing regimen.

*Safety Data.* As of the data cutoff date, QD dosing of BLU-667 was observed to be well-tolerated. The MTD for BLU-667 was determined to be 400 mg QD using a Bayesian optimal interval design. At QD dose levels up to and including the MTD, the majority of AEs reported by investigators were Grade 1 or 2. AEs reported by investigators ( $\geq 20$  percent) most commonly included constipation (24 percent), increased alanine aminotransferase (ALT) (22 percent) and increased aspartate aminotransferase (20 percent). Investigators reported treatment-related Grade 3 AEs in eight patients (16 percent). Treatment-related Grade 3 AEs occurring in two or more patients included hypertension and neutropenia. There were no treatment-related Grade 4 or 5 AEs.

Across all QD dose levels up to 600 mg QD, seven patients experienced dose-limiting toxicities. Only one patient discontinued treatment with BLU-667 due to a dose-limiting toxicity (Grade 3 ALT increase). An additional 11 patients discontinued treatment, including eight patients due to progressive disease, one patient due to an AE unrelated to BLU-667 and one patient due to non-compliance. One patient passed away, and the death was deemed unrelated to BLU-667. Among all 53 enrolled patients, 41 patients (77 percent) remained on BLU-667 as of the data cutoff date. Duration of treatment ranged from 0.3 to 11.5 months.

*Clinical Activity Data.* As of the data cutoff date, 40 patients with RET-altered tumors were evaluable for response assessment, including 14 patients with NSCLC, 25 patients with MTC and one patient with PTC. CT and MRI imaging was used to measure clinical activity by RECIST version 1.1. Of the remaining 13 enrolled patients who were not evaluable for response assessment, two patients did not have RET-altered tumors, one patient died due to an AE unrelated to BLU-667 prior to any response assessment and 10 recently enrolled patients had not been evaluated for response by the data cutoff date. Across all evaluable patients, the preliminary ORR was 45 percent. Responses were observed in patients previously treated with multi-kinase therapy, immunotherapy and chemotherapy.

*RET-altered NSCLC*

- 85% of NSCLC patients with measurable target lesions had radiographic tumor reductions.
- Seven patients achieved a PR (five confirmed, two pending confirmation), representing a preliminary ORR of 50 percent.
- Responses were observed in patients with the most common RET alterations in NSCLC, including RET-KIF5B and RET-CCDC6 fusions.
- Preliminary evidence of anti-tumor activity in the brain was observed in metastatic NSCLC.

*RET-altered MTC*

- 83% of MTC patients with measurable target lesions had radiographic tumor reductions.
- One patient achieved a confirmed complete response, nine patients achieved a PR (five confirmed, four pending confirmation), representing a preliminary ORR of 40 percent.

- Responses were observed in patients with the most common activating RET mutations in MTC, including the RET-M918T mutation.

*Other RET-altered solid tumors*

- One patient with RET-altered PTC achieved a PR (pending confirmation).

*Phase 1 ARROW Trial—Thyroid Cancer Data Reported in September 2018 at the ATA Annual Meeting*

The data presented included all patients enrolled in the Phase 1 ARROW clinical trial as of May 9, 2018, and included follow-up on these patients through the data cutoff date of September 14, 2018. Of the 69 patients who had been treated with BLU-667 in the dose escalation and expansion portions of the trial, 42 had RET-altered thyroid cancer, including 37 with MTC and five with PTC. In the dose escalation portion, patients were treated at dose levels ranging from 30 mg to 600 mg QD or up to 300 mg twice daily. In the expansion portion, patients were treated at the recommended phase 2 dose of 400 mg QD.

*Safety Data.* The reported data showed that across 69 patients, BLU-667 was well-tolerated as of the data cutoff date. Most AEs were Grade 1, and only two patients discontinued therapy due to a treatment-related AE (Grade 3 increased alanine aminotransferase in a patient with liver metastases and Grade 2 pneumonitis). Treatment-emergent AEs (regardless of relationship to BLU-667) reported by investigators ( $\geq 15$  percent) most commonly were constipation (35 percent), increased aspartate aminotransferase (33 percent), anemia (30 percent), hypertension (30 percent), decreased white blood cell count (29 percent), diarrhea (28 percent), neutropenia (28 percent), increased alanine aminotransferase (25 percent), increased blood creatinine (23 percent), fatigue (19 percent) and headache (17 percent). Grade 3 or higher treatment-related AEs occurring in two or more patients included anemia, hypertension, decreased white blood cell count, diarrhea and neutropenia.

*Clinical Activity Data.* As of the data cutoff date, 35 patients with MTC and four patients with PTC were evaluable for response assessment by RECIST version 1.1. Overall, 90 percent of MTC and PTC patients with measurable target lesions had radiographic tumor reductions.

In patients with MTC, response assessments showed increased clinical activity with higher dose levels and longer treatment durations. Across all evaluable MTC patients, the overall response rate (ORR) was 49 percent, including one patient with a confirmed CR and 16 patients with a PR (two pending confirmation). In patients with MTC treated with 300 to 400 mg QD for at least 24 weeks, the response rate was 62 percent, including one patient with a confirmed CR and seven patients with a confirmed PR.

In patients with PTC, two of four evaluable patients had a confirmed PR, and all evaluable patients with PTC had radiographic tumor shrinkage.

The data also showed encouraging evidence of durable activity. All patients with MTC and PTC who responded to BLU-667 remain on treatment as of the data cutoff date. In addition, all patients treated at 400 mg QD were continuing on therapy as of the data cutoff date. Patients with the longest treatment durations remained on therapy for more than 15 months.

Anti-tumor activity was observed regardless of prior MKI therapy or RET alteration. Similar response rates were observed in MTC patients who were MKI-experienced (47 percent; 8/17 patients) and MKI-naïve (50 percent; 9/18 patients). In addition, clinical responses were observed in patients with common activating mutations in MTC (e.g., M918T) and fusion partners in PTC (e.g., NCO4A and CCDC6). A clinical response was also observed in the one evaluable MTC patient with a germline V804M gatekeeper mutation.

*ARROW Trial Design.* ARROW is a Phase 1 clinical trial designed to evaluate the safety, tolerability and efficacy of BLU-667 in multiple ascending doses in adults with RET-altered NSCLC, MTC and other advanced solid tumors. The trial consists of two parts: a dose escalation portion and an expansion portion. Enrollment in the dose escalation portion is complete, and the expansion portion has been initiated and is actively enrolling patients in seven defined cohorts at the recommended phase 2 dose of 400 mg QD: (1) RET-fusion NSCLC patients previously treated with platinum-based chemotherapy, (2) RET-fusion NSCLC patients who have not previously received any platinum-based chemotherapy, (3) MTC patients previously treated with an MKI, (4) MTC patients who have not previously

received any MKI treatment, (5) patients with RET-fusion solid tumors previously treated with the prior standard of care for their tumor type, (6) patients with RET-altered solid tumors previously treated with a selective RET tyrosine kinase inhibitor and (7) patients with RET-mutated solid tumors previously treated with the stand of care for their tumor type. Trial objectives include assessing response, pharmacokinetics, pharmacodynamics and safety. The trial is designed to enroll approximately 360 patients across all six expansion cohorts at multiple sites in the United States, European Union and Asia.

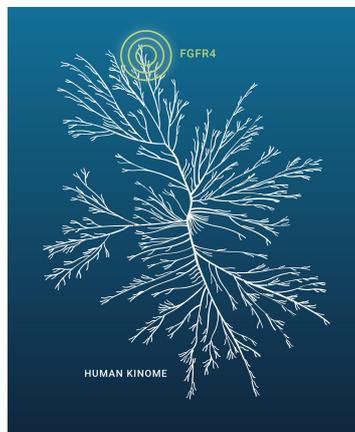
*Data Reported in September 2018 at the World Lung Conference*

The data presented at the World Lung Conference and in *Cancer Discovery* included pre-clinical data and two clinical cases highlighting the potential of combining BLU-667 and osimertinib to overcome treatment resistance in EGFR-mutant NSCLC. The clinical cases included two patients treated with BLU-667 and osimertinib under investigator-sponsored protocols. The patients had advanced EGFR-mutant NSCLC that progressed on standard targeted therapy, with an acquired RET fusion identified via lung biopsy. Radiographic scans after eight weeks showed both patients experienced a partial response (both pending confirmation), with each achieving a 78 percent reduction in target tumors per RECIST version 1.1. The combination was well tolerated, and all reported adverse events were Grade 1 or 2. Both patients continued to receive treatment as of September 26, 2018.

**FGFR4 Inhibitor Program**

*Overview*

BLU-554 is an orally available, potent, selective and irreversible inhibitor of the kinase FGFR4. FGFR4 functions as a receptor whose aberrant activation is a driver of HCC. FGFR4 belongs to a family of highly homologous receptors, which include FGFR1-4. BLU-554 targets FGFR4, while sparing the other three FGFR paralogs, and demonstrates exquisite kinome selectivity. Pre-clinical *in vitro* and *in vivo* efficacy data provides a strong rationale for the development of BLU-554 for the subset of HCC patients whose tumors are driven by aberrant FGFR4 signaling. We estimate that approximately 30% of patients with HCC have tumors with aberrantly activated FGFR4 signaling, which we refer to as FGFR4-activated HCC.



Approximate kinome tree location of FGFR4. Each branch of the dendrogram represents an individual human kinase. *Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc., or CSTI (www.cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.*

*HCC Disease Background*

Liver cancer is the second leading cause of cancer-related deaths worldwide, and HCC accounts for most liver cancers. The highest incidence of HCC occurs in regions with endemic hepatitis B virus, or HBV, including Southeast Asia and sub-Saharan Africa. In the United States, HCC is the fastest rising cause of cancer-related death. Over the past two decades, the incidence of HCC has tripled while the five-year survival rate has remained below 12%.

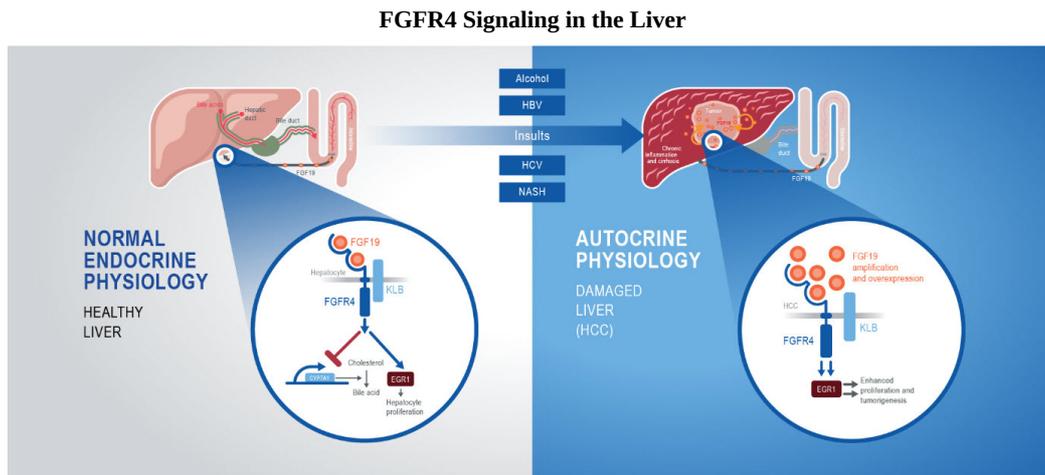
Cirrhosis is a key risk factor for HCC — the disease etiology varies by geography with the common theme of chronic conditions that lead to cirrhosis. In North America, the main risk factors for cirrhosis are infection with hepatitis C virus, or HCV, followed by HBV infection, alcohol consumption and nonalcoholic steatohepatitis. In the European Union, the main risk factors for cirrhosis are HCV, HBV and alcohol consumption. In Asia and sub-Saharan Africa, the major risk factor is chronic HBV infection.

The diagnosis of HCC is typically made in adults, peaking around age 70. Disease management is complicated by concurrent liver disease, which often compromises liver function in these patients. Patients are staged depending on extent of liver disease, performance status and liver function status; these factors guide treatment selection. The stage distribution at diagnosis varies by region. Countries with active national screening programs, such as Taiwan and Japan, tend to diagnose many more patients in the early stages of disease. There are currently no treatments for molecularly defined patient subgroups in HCC.

Despite advances in the treatment of HCC, including the recent approvals of nivolumab, pembrolizumab and levatinib, the prognosis for patients with advanced HCC remains poor, and there is a significant unmet need for new treatments for HCC, including FGFR4-driven HCC. Patients diagnosed at an early stage receive potentially curative transplant, resection or ablative therapies. Treatments for intermediate to advanced stage patients include high-dose chemotherapy delivered directly to the liver (transarterial chemoembolization), the multi-kinase inhibitors sorafenib, regorafenib, cabozantinib and levatinib, and the immunotherapies nivolumab and pembrolizumab. There are no approved treatments that selectively target FGFR4. Sorafenib and levatinib have overall response rates of 2% and 19%, respectively, in treatment-naïve patients. Nivolumab, pembrolizumab, regorafenib and cabozantinib have overall response rates ranging from 4 to 17% in patients previously treated with or intolerant to sorafenib. In clinical practice, patients often require dose modifications or discontinue therapy with multi-kinase inhibitors due to tolerability issues. There is a clear need for medical therapies with a favorable risk-benefit profile and the potential be used alone or in combination with other approved or emerging therapies for advanced HCC.

### *FGFR4 as a Driver in HCC*

The FGFR4 signaling pathway is a promising new driver for the development of molecularly targeted therapy in HCC. The link between aberrant FGFR4 signaling and HCC was first established when an amplicon, a region of replicated DNA, that includes FGF19, the ligand that activates FGFR4, was identified in HCC patients. We estimate that more than 5% of tumors of HCC patients have this amplicon. The physiologic role of the receptor, FGFR4, and its ligand, FGF19, is to regulate bile acid metabolism in hepatocytes and liver regeneration following injury. FGF19 is normally produced in the small intestine and signals to hepatocytes through an endocrine mechanism. FGF19 forms an active signaling complex together with FGFR4 and its co-receptor Klotho- $\beta$ . Signaling of the active complex leads to decreased CYP7A1 transcription with a resultant decrease in bile acid synthesis, as well as increased growth, proliferation and survival signals.



In the figure above, HBV means hepatitis B virus, HCV means hepatitis C virus, NASH means non-alcoholic steatohepatitis and KLB means Klotho- $\beta$ .

Subsequent data suggest that FGFR4 signaling is a driver in a subset of HCC patients in whom the pathway is aberrantly activated. In these patients, FGF19 is overexpressed in hepatocytes (which do not normally express FGF19), leading to autocrine signaling and tumor growth. Pre-clinical experiments in a genetically engineered mouse model demonstrate that exogenous FGF19 expression is sufficient to induce liver tumor growth and that tumorigenesis is dependent on FGFR4. The three elements that constitute an active FGFR4 signaling complex, FGF19, FGFR4 and Klotho- $\beta$ , are expressed together uniquely in HCC, although it is possible that they may also occur in rare cases of other solid tumors.

We have used our novel drug discovery platform to identify a potentially broader target responder population in addition to the FGF19-amplified patient population. We estimate that approximately 25% of HCC tumors overexpress FGF19 without amplification. We have also demonstrated a significant anti-tumor response with an FGFR4 inhibitor in an HCC patient-derived xenograft model that overexpresses FGF19 in the absence of amplification. Some of these results were published in *Cancer Discovery* in 2015. We estimate that approximately 30% of patients have FGFR4-activated HCC, and data suggest patients with HCC patients with FGFR4 pathway activation resulting in activation of the FGFR4 pathway generally have poor outcomes relative to other HCC patients.

#### **BLU-554 – Clinical Development for Patients with Advanced HCC**

We are currently evaluating BLU-554 in an ongoing Phase 1 clinical trial in patients with advanced HCC. In October 2017, we presented updated data from this ongoing clinical trial at European Society of Medical Oncology 2017 Congress, or ESMO Meeting.

Under our collaboration with CStone, the China National Medicinal Products Administration has approved an IND application for our ongoing Phase 1 trial of BLU-554 in advanced hepatocellular carcinoma, and we and CStone plan to expand this trial to include clinical sites in Mainland China by the middle of 2019. In addition, we and CStone plan to initiate a proof-of-concept clinical trial in the second half of 2019 in the CStone territory evaluating BLU-554 in combination with CS1001, a clinical stage anti-programmed death ligand-1 immunotherapy being developed by CStone, as a first-line therapy for the treatment of patients with HCC. See “—Collaborations” below for more information.

The FDA has granted orphan drug designation to BLU-554 for the treatment of HCC.

#### *Phase 1 Trial—Data Reported in October 2017 at the ESMO Annual Meeting*

As of the data cutoff of August 18, 2017, 77 patients had been treated with BLU-554 in the dose escalation and expansion portions of the Phase 1 clinical trial at five dose levels (ranging from 140 mg QD to 900 mg QD), including 44 patients with FGFR4-activated HCC. FGFR4-activated HCC was defined as at least one percent tumor expression of FGF19, the FGFR4 ligand, as measured by an immunohistochemistry, or IHC, assay. In general, the enrolled population was heavily pretreated: 82% received prior TKI treatment, 23% received prior immunotherapy and 91% received prior systemic therapy. PK analysis demonstrated rapid oral absorption across all dose levels, with a mean half-life of approximately 17 hours and exposure in the expected therapeutic range based on HCC xenograft models. Collectively, we believe that these data support a once-daily dosing regimen.

*Safety Data.* As of the data cutoff of August 18, 2017, the majority of AEs reported by investigators were Grade 1 or 2. Across all grades, the most common AEs reported by investigators related to BLU-554 included diarrhea (71%), nausea (42%), vomiting (36%), transaminase elevation (AST 34% and ALT 32%) and fatigue (29%). Grade 3 or higher AEs related to BLU-554 occurring in five or more patients included anemia, diarrhea and transaminase elevation (AST and ALT). Among all 77 patients treated with BLU-554, 58 patients discontinued treatment with BLU-554, including 42 patients due to disease progression, 11 patients due to treatment-related AEs, three patients who withdrew consent and two patients due to the investigator’s decision.

*Clinical Activity Data.* As of the data cutoff of August 18, 2017, 67 patients were evaluable for response assessment. An additional 10 patients were treated with BLU-554 as of the data cutoff date but were not evaluable for response assessment. Response was assessed using RECIST version 1.1.

In patients with FGFR4-activated HCC (n=38), the data showed an ORR of 16% (95% confidence interval 6-31%). In addition, 49% of patients had radiographic tumor reduction, and clinical activity was observed regardless of disease etiology or geography. As of the data cutoff date:

- One patient had an unconfirmed complete response.
- Five patients had a partial response, with four confirmed and one unconfirmed.
- An additional 20 patients had stable disease, representing a disease control rate of 68%.
- No responses were observed in patients without FGFR4 pathway activation (n=29).

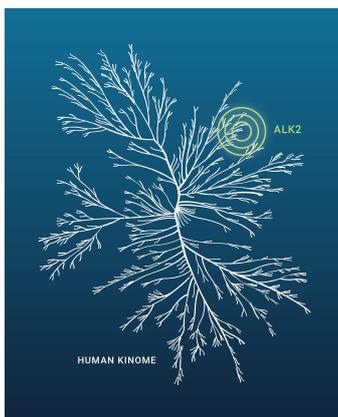
Among all 77 patients treated with BLU-554, 19 remained on treatment as of the data cutoff date, including 15 patients with FGFR4-activated HCC. Median progression-free survival was 3.7 months among patients with FGFR4-activated HCC.

In addition, five TKI-naïve patients with FGFR4-activated HCC were evaluable for response assessment as of the data cutoff date. Within this group, preliminary evidence of prolonged disease control was observed. Two TKI-naïve patients remain on treatment as of the data cutoff date with a duration of treatment of 11.4 months and 12.3 months, respectively.

*Phase 1 Clinical Trial Design.* This Phase 1 clinical trial is designed to evaluate the safety and tolerability of BLU-554 in adults with advanced HCC. The trial consists of two parts: a dose escalation portion and an expansion portion. We have completed the dose escalation portion, and patient enrollment in the dose expansion portion is currently ongoing at the MTD of 600 mg QD. The expansion portion of the trial is designed to enroll patients in the following cohorts: (1) three subsets of patients with HCC, regardless of prior therapy, and (2) patients with FGFR4-activated HCC who have not been previously treated with a TKI, which we refer to as the TKI-naïve cohort. We are currently only enrolling patients in the TKI-naïve cohort of the expansion portion of this clinical trial. The primary objective of the expansion portion of the Phase 1 clinical trial is to continue to evaluate the safety and tolerability of BLU-554. Secondary objectives include assessing clinical activity by RECIST version 1.1, as well as evaluating the PK of BLU-554 and pharmacodynamic markers of BLU-554 activity. The Phase 1 clinical trial is designed to enroll approximately 150 patients, including approximately 40 patients during dose escalation and approximately 110 patients across both expansion cohorts, at multiple sites in the United States, European Union and Asia.

### **Fibrodysplasia Ossificans Progressiva (FOP)**

BLU-782 is an orally available, potent and highly selective inhibitor that targets mutant ALK2. We are developing BLU-782 for the treatment of FOP, a rare, severely disabling genetic disease caused by mutations in the ALK2 gene, ACVR1. FOP is characterized by progressive heterotopic ossification, which is the abnormal transformation of muscle, ligaments and tendons into bone. Heterotopic ossification may be spontaneous or associated with painful episodic disease flare-ups that are usually precipitated by soft tissue injury. As the disease progresses, extra-skeletal bone increasingly restricts joints, resulting in severe disability and loss of mobility, compromised respiratory function and increased risk of early death. Currently, there are no approved therapies for FOP.



Approximate kinome tree location of ALK2. Each branch of the dendrogram represents an individual human kinase. *Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc., or CSTI (www.cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.*

We initiated a Phase 1 clinical trial in healthy volunteers in the first quarter of 2019, and we plan to initiate a Phase 2 clinical trial evaluating BLU-782 in patients with FOP in the first half of 2020. In October 2018, we presented foundational pre-clinical data at the 2018 American Society for Bone and Mineral Research, or ASBMR, Annual Meeting. The FDA has granted fast track designation to BLU-782 for the treatment of fibrodysplasia ossificans progressiva.

#### *BLU-782 Pre-Clinical Data Presented at the ASBMR Annual Meeting*

In the preclinical data presented at the ASBMR Annual Meeting, BLU-782 demonstrated exquisite selectivity for R206H mutant ALK2 in cellular assays, while sparing closely related anti-targets including ALK1, ALK3, and ALK6. Additionally, BLU-782 potently inhibited mutant ALK2 *in vitro*, regardless of the activating ligand, including Activin A, Activin B and BMP6. In *in vivo* studies in a conditional knock-in ALK2<sup>R206H</sup> transgenic mouse model showed BLU-782 prevented the formation of injury-induced heterotopic ossification, or HO, and edema, as measured by micro computed tomography and magnetic resonance imaging. IHC analyses also showed restoration of a healthy response to tissue injury in ALK2<sup>R206H</sup> mice, including skeletal myofiber regeneration. In addition, BLU-782 prevented the formation of surgery-induced HO following fibular osteotomy surgery in ALK2<sup>R206H</sup> mice.

#### **Collaborations**

##### **Roche**

In March 2016, we entered into the Roche agreement pursuant to which we and Roche have agreed to collaborate on the discovery, development and commercialization of up to five small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy, as single products or possibly in combination with other therapeutics. The parties are currently conducting activities for up to five programs under the collaboration, including up to two collaboration programs leveraging our novel target discovery engine and proprietary compound library to select potential targets.

Under the Roche agreement, Roche is granted up to five option rights to obtain an exclusive license to exploit products derived from the collaboration programs, or licensed products, in the field of cancer immunotherapy. Such option rights are triggered upon the achievement of Phase 1 proof-of-concept. For up to three of the five collaboration programs, if Roche exercises its option, Roche will receive worldwide, exclusive commercialization rights for the licensed products. For up to two of the five collaboration programs, if Roche exercises its option, we will retain commercialization rights in the United States for the licensed products, and Roche will receive commercialization rights outside of the United States for the licensed products. 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 will have the lead responsibility for drug discovery and pre-clinical development of all collaboration programs. In addition, we 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 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 we and Roche will share post-Phase 1 development costs for each licensed product for which we retain commercialization rights in the United States.

We received an upfront cash payment of \$45.0 million in March 2016 upon execution of the Roche agreement, and subject to the terms of the Roche agreement, we will be eligible to receive up to approximately \$965.0 million in contingent option fees and milestone payments related to specified research, pre-clinical, clinical, regulatory and sales-based milestones. Of the total contingent payments, up to approximately \$215.0 million are for option fees and milestone payments for research, pre-clinical and clinical development events prior to licensing across all five potential collaboration programs, including contingent milestone payments for initiation of each of the collaboration programs for which the parties will work together to select targets. In June 2018, we achieved and received a \$10.0 million research milestone payment. 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 United States, 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 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 agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the Roche 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 United States for the collaboration programs on which we will retain rights in the United States, with Roche receiving a license under our intellectual property to develop and commercialize such licensed products outside of the United States.

Subject to the terms and conditions of the Roche agreement, we have agreed to work exclusively with Roche with respect to each collaboration target. In the third quarter of 2018, our obligation to work exclusively with Roche within the field of cancer immunotherapy expired under the terms of the Roche agreement. 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 under either of the collaboration programs for which we will retain commercialization rights in the United States. 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 agreement or certain agreements with contract research organizations, contract manufacturing organizations, academic institutions, not-for-profit third parties or distributors.

The Roche 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 agreement. Prior to its exercise of its first option, Roche may terminate the Roche 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 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 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.

### ***CStone Pharmaceuticals***

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 our drug candidates BLU-554, avapritinib, and BLU-667, including back-up forms and certain other forms thereof, which we refer to collectively as the licensed products, in Mainland China, Hong Kong, Macau and Taiwan, each of which we refer to as a "region" and collectively, as 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 subject to the terms of the CStone agreement, will be eligible to receive up to approximately \$346.0 million in milestone payments, including \$118.5 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 BLU-554 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 will be 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 after June 1, 2019, 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.

## **Intellectual Property**

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our drug candidates, including avapritinib, BLU-667, BLU-554 and BLU-782, and 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 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. 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 February 15, 2019, we owned 21 issued U.S. patents, 21 pending U.S. patent applications, nine pending U.S. provisional applications, 167 foreign patent applications pending in a number of jurisdictions, including Australia, Brazil, Canada, China, the European Union, Israel, India, Japan, South Korea, Mexico New Zealand, Russia, South Africa, 13 issued foreign patents, and four pending Patent Cooperation Treaty, or PCT, international patent applications. Our pending patent applications pertain to our key research and development programs, specifically our programs for avapritinib, BLU-667, BLU-554 and BLU-782, and our pipeline, including additional kinase discovery programs and novel recurrent fusions. Our issued U.S. patents are projected to expire between 2033 and 2037, and any patents that may issue from our pending U.S. applications and provisional U.S. applications would be projected to expire between 2033 and 2040.

The intellectual property portfolios for our most advanced drug candidates as of February 15, 2019 are summarized below. Each of these portfolios is in its early stages and, with respect to some of the pending patent applications covering our drug candidates, prosecution has just begun or is in progress. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the 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.

***Avapritinib (KIT and PDGFRA)***

The intellectual property portfolio for our avapritinib program contains patent applications directed to compositions of matter for avapritinib and analogs, compositions of matter for KIT inhibitors with different compound families, as well as methods of use for these novel compounds. As of February 15, 2019, we owned nine issued US patents, three pending U.S. patent applications, 40 pending foreign patent applications in a number of jurisdictions, including Argentina, Australia, Bolivia, Brazil, Canada, China, the European Union, Israel, India, Japan, South Korea, Mexico, New Zealand, Pakistan, Russia, South Africa, Taiwan and Venezuela, four issued foreign patents, one pending PCT international patent application and two U.S. provisional applications directed to our KIT and PDGFRA program, including avapritinib. Any U.S. or ex-U.S. patents issuing from the pending applications covering avapritinib will have a statutory expiration date of October 2034 or January 2040. Patent term adjustments or patent term extensions could result in later expiration dates.

***BLU-667 (RET)***

The intellectual property portfolio for our BLU-667 program contains patent applications directed to compositions of matter for BLU-667 and analogs, compositions of matter for RET inhibitors with different compound families and methods of use for these novel compounds. As of February 15, 2019, we owned four issued U.S. patents, three pending U.S. patent applications, one pending PCT international application, 28 pending foreign patent applications in a number of jurisdictions, including the United Arab Emirates, Argentina, Australia, Brazil, Canada, China, the European Union, Israel, India, Japan, Saudi Arabia, South Korea, Mexico, New Zealand, Eurasia and South Africa, and six pending provisional U.S. patent applications directed to our RET program, including BLU-667, which, if issued, will have statutory expiration dates between November 2036 and August 2039.

***BLU-554 (FGFR4)***

The intellectual property portfolio for our BLU-554 program contains patent applications directed to compositions of matter for BLU-554 and analogs, as well as compositions of matter for FGFR4 inhibitors with different compound families. The portfolio also includes patent applications directed to methods of use for the novel compounds as well as patent applications directed broadly to FGFR4 selective inhibitors. As of February 15, 2019, we owned seven issued U.S. patents, two pending U.S. patent applications, one pending PCT international application, 39 foreign patent applications pending in a number of jurisdictions, including Australia, Brazil, Canada, China, the European Union, Israel, India, Japan, South Korea, Mexico, New Zealand, Russia, South Africa and Taiwan, and eight issued foreign patents directed to our FGFR4 program, including BLU-554. Any U.S. or ex-U.S. patent issuing from the pending applications covering BLU-554 will have a statutory expiration date between July 2033 and September 2037. Patent term adjustments or patent term extensions could result in later expiration dates.

***BLU-782 (ALK2)***

The intellectual property portfolio for our BLU-782 program contains patent applications directed to compositions of matter for BLU-782 and analogs, compositions of matter for other inhibitors with different compound families and methods of use for these novel compounds. As of February 15, 2019, we owned one pending U.S. patent application, one pending PCT international application and 15 pending foreign patent applications in a number of jurisdictions, including Australia, Brazil, Canada, China, Chile, the European Union, Israel, Japan, South Korea, Mexico, New Zealand, Eurasia and South Africa, directed to our ALK2 program, including BLU-782, which, if issued, will have statutory expiration dates of April 2037 or October 2038.

***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 February 15, 2019, we owned ten pending U.S. patent applications, nine pending European Union patent applications and one issued European patent directed to this technology, which, if issued, will have statutory expiration dates ranging from 2034 to 2039.

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 United States, the patent term is 20 years from the earliest filing date of a

non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or 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 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 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 United States 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 candidate we may develop, it is possible that, before any of our 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 and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We have also executed agreements requiring assignment of inventions with selected scientific advisors 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. Any 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 genetic 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, pre-clinical 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 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.

If our drug candidates are approved for the indications for which we are currently conducting or planning clinical trials, they will compete with the drugs discussed below and will likely compete with other drugs that are currently in development.

#### **avapritinib**

We are initially developing avapritinib for advanced GIST and for SM, including advanced SM and indolent and smoldering SM. If avapritinib receives marketing approval for advanced SM, it will face competition from Novartis AG's midostaurin, a multi-kinase inhibitor with KIT D816V inhibitory activity that was approved in April 2017 by the FDA for the treatment of advanced SM. If avapritinib receives marketing approval for third line advanced GIST, it will face competition from Bayer AG's regorafenib, and if avapritinib receives marketing approval for second line advanced GIST, it will face competition from Pfizer Inc.'s sunitinib. In addition, if avapritinib receives marketing approval for advanced SM, GIST and/or for GIST patients with the PDGFRA D842V mutation, it may face competition from other drug candidates in development for these indications, including drug candidates in development by AB Science S.A., Allakos Inc., ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AROG Pharmaceuticals, Inc., Celldex Therapeutics, Inc., and Deciphera Pharmaceuticals, LLC.

#### **BLU-667**

We are initially developing BLU-667 for patients with RET-altered NSCLC, MTC and other advanced solid tumors. If BLU-667 receives marketing approval for patients with RET-driven cancers, it may face competition from other drug candidates in development, including drug candidates in development by ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AstraZeneca plc, Boston Pharmaceuticals, Inc., Eisai Inc., Exelixis, Inc., GlaxoSmithKline plc, Loxo Oncology, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Mirati Therapeutics, Inc., Novartis AG, Pfizer Inc. and Roche, as well as several approved multi-kinase inhibitors with RET activity being evaluated in clinical trials, including alectinib, apatinib, cabozantinib, dovitinib, lenvatinib, ponatinib, sorafenib, sunitinib and vandetinib.

#### **BLU-554**

We are initially developing BLU-554 for patients with advanced HCC driven by FGFR4. If BLU-554 receives marketing approval for patients with FGFR4-activated HCC, it will face competition from Bristol-Myers Squibb Company's nivolumab and Merck & Co., Inc.'s pembrolizumab, immune checkpoint inhibitors approved by the FDA for the treatment of HCC, as well as sorafenib, cabozantinib, regorafenib and lenvatinib, multi-kinase inhibitors approved for the treatment of HCC. In addition, BLU-554 may face competition from other drug candidates in development by Abbisko Therapeutics Co., Ltd, AstraZeneca plc, Bayer AG, Celgene Corporation, Eisai Inc., H3 Biomedicine Inc., Incyte Corporation, Johnson & Johnson, Novartis AG, Sanofi S.A., Taiho Pharmaceutical Co., Ltd., U3 Pharma GmbH, a wholly-owned subsidiary of Daiichi Sankyo Company, Limited, and Xoma Ltd.

## **BLU-782**

We are initially developing BLU-782 for patients with FOP. If BLU-782 receives marketing approval for FOP, it may face competition from drug candidates in development by BioCryst Pharmaceuticals, Inc., Clementia Pharmaceuticals Inc., La Jolla Pharmaceutical Company and Regeneron Pharmaceuticals, Inc.

### ***Commercialization Plans***

Our goal is to become a fully-integrated precision therapy company capable of delivering transformative precision therapies to patients. Given our stage of development, we have started to establish our own commercial organization and distribution capabilities with an initial focus on the United States and Europe. We believe our portfolio strategy focused on genomically defined cancers, rare diseases and cancer immunotherapy will allow us to efficiently commercialize our drug candidates in the United States and Europe on our own initially and worldwide longer-term. We currently have worldwide development and commercialization rights to avapritinib, BLU-667 and BLU-554 other than the rights licensed to CStone in the CStone territory, and we currently have worldwide development and commercialization rights to BLU-782 and all of our discovery programs other than the discovery-stage programs under the Roche collaboration. Subject to obtaining regulatory approval, we believe we can successfully launch and commercialize our initial drug candidates on our own, using a small and highly specialized sales force similar to those of other rare disease companies. However, we may establish collaborations with pharmaceutical companies to leverage their capabilities to maximize the potential of our drug candidates.

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 for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-667 in order to identify NSCLC patients with RET fusions and BLU-554 in order to identify HCC patients with FGFR4 pathway activation.

### ***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 pre-clinical and clinical testing, as well as for commercial manufacture of any drugs that we may commercialize. To date, we have obtained active pharmaceutical ingredients, or API, or drug substance for avapritinib, BLU-667, BLU-554 and BLU-782 for our pre-clinical and clinical testing from four third-party manufacturer and drug product from two 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. We do not currently have arrangements in place for redundant supply for commercial API and drug substance or for clinical and commercial drug product. For all of our drug candidates, we intend to identify and qualify additional manufacturers to provide the API, drug substance and drug product prior to submission of a new drug application to the FDA and/or a marketing authorization application to the European Medicines Agency.

Our drug candidates avapritinib, BLU-667, BLU-554 and BLU-782 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, we will rely on third parties to develop and commercialize companion diagnostic tests for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-667 in order to identify NSCLC patients with RET fusions and BLU-554 in order to identify HCC patients with FGFR4 pathway activation. 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 United States 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 United States, 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 United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of extensive nonclinical tests, sometimes referred to as pre-clinical laboratory tests, animal studies and formulation studies performed in accordance with applicable regulations, including the FDA's 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 annual 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;
- 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 requirements, or cGMP;
- potential FDA audit of the pre-clinical 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 United States.

The data required to support an NDA is generated in two distinct development stages: pre-clinical and clinical. For new chemical entities, the pre-clinical 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 pre-clinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the pre-clinical 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 pre-clinical data, general investigational plan and the protocol(s) for human trials. The IND automatically 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.

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 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 adverse effects 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.

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.

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 pre-clinical 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 pre-clinical and clinical testing. The application includes both negative or ambiguous results of pre-clinical 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 United States.

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 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 2019 fee schedule, effective through September 30, 2019, the user fee for an application requiring clinical data, such as an NDA, is \$2,588,478. PDUFA also imposes an annual prescription drug product program fee for human drugs (\$309,915). 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 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. 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, pre-clinical 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 United States 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 pre-clinical 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 product 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 pre-clinical 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 (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 United States, 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 testing, sometimes referred to as Phase 4 testing, 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 United States, 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 United States, 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 subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, voluntary recalls, seizure of drugs, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. 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.

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 voluntary 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.

#### *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 United States 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 pre-clinical 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 United States. 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 United States, or if it affects more than 200,000 individuals in the United States, 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 United States. In the European Union, 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 European Union 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 and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. 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 European Union, 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.

#### *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 for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-667 in order to identify NSCLC patients with RET fusions and BLU-554 in order to identify HCC patients with FGFR4 pathway activation. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, pre-clinical 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, pre-clinical, 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 EEA, *in vitro* medical devices are required to conform with the essential requirements of the E.U. Directive on *in vitro* diagnostic medical devices (Directive No 98/79/EC, as amended). To demonstrate compliance with the essential 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 EEA 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 EEA.

### ***European Drug Development***

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

Similar to the United States, the various phases of pre-clinical and clinical research in the European Union are subject to significant regulatory controls. Although the current EU Clinical Trials Directive 2001/20/EC, or Clinical Trials Directive, has sought to harmonize the European Union clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the European Union, the European Union Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the European Union countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, or the Clinical Trials Regulation, which is set to replace the Clinical Trials Directive. It is expected that the new Clinical Trials Regulation will apply by October 2019. The Clinical Trials Regulation will overhaul the current system of approvals for clinical trials in the European Union. Specifically, the new legislation, which will be directly applicable in all member states, 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 European Economic Area, or EEA, (which is comprised of the 28 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the EMA and which is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of drugs, such as biotechnology medicinal drugs, orphan medicinal drugs, and medicinal drugs containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for drugs containing a new active substance not yet authorized in the EEA, or for drugs that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for drugs not falling within the mandatory scope of the Centralized Procedure. Where a drug has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member State through the Mutual Recognition Procedure. If the drug 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. The competent authority of the RMS prepares a draft assessment report, a draft

summary of the drug characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the drug is subsequently granted a national MA in all the Member States (i.e. in the RMS and the Member States Concerned).

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

#### *European Chemical Entity Exclusivity*

In the European Union, 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 European Union from referencing the innovator's data to assess a generic application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved 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.

#### **Rest of the World Regulation**

For other countries outside of the European Union and the United States, 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.

#### **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. 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 Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the Affordable Care Act, enacted in March 2010, 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% 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 United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, started in April 2013, and, due to subsequent legislative amendments, will stay in effect through 2025 unless additional Congressional action is taken. On January 2, 2013, then President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare drugs and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the Affordable Care Act. The 2017 Tax Cuts and Jobs Act, or TJCA, includes a provision repealing the individual mandate, effective January 1, 2019. Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. 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. In addition, the Centers for Medicare & Medicaid Services, the agency responsible for administering the Medicare program, or CMS, recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the health benefits required under the Affordable Care Act for plans sold through these marketplaces. There may be further action to repeal, replace or modify the Affordable Care Act. 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, 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 European Union 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 United States 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 product 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 products 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.

The federal Health Insurance Portability and Accountability Act of 1996, or 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.

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 of up to an aggregate of \$150,000 per year (or up to an aggregate of \$1 million per year for

“knowing failures”), 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 Centers for Medicare & Medicaid Services, which publicly posts the data on its website. 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, or 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.

## **Employees**

As of February 15, 2019, we had 217 full-time employees, including 76 employees with M.D. or Ph.D. degrees. Of these full-time employees, 159 employees are engaged in research and development activities. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

## **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>.

## 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. Please see page 1 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. 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 Our Financial Position and Need for Additional Capital**

***We are a precision therapy company with a limited operating history and have not generated any revenue from drug sales. 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 on which investors can base an investment decision. Biopharmaceutical drug development is a highly speculative undertaking and involves a substantial degree of risk. We commenced operations in April 2011. Our operations to date have been limited primarily to organizing and staffing our company, business planning, raising capital, developing our technology, identifying potential drug candidates and undertaking pre-clinical studies and commencing Phase 1 clinical trials and preparing for additional planned clinical trials for our most advanced drug candidates, avapritinib, BLU-667, BLU-554 and BLU-782.

We have not yet demonstrated our ability to successfully complete any clinical trials, including large-scale, pivotal clinical trials, obtain regulatory approvals, manufacture a commercial scale drug, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes many years to develop one new drug from the time it is discovered to when it is available for treating patients. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history. We will need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Since inception, we have focused substantially all of our efforts and financial resources 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, producing drug substance and drug product material for use in pre-clinical studies and clinical trials, conducting pre-clinical studies and commencing clinical development and pre-commercial activities. To date, we have financed our operations primarily through public offerings of our common stock, private placements of our convertible preferred stock, collaborations and a debt financing. Through December 31, 2018, we have received an aggregate of \$1.1 billion from such transactions, including \$887.4 million in aggregate gross proceeds from the sale of common stock in our May 2015 initial public offering, or IPO, and December 2016, April 2017 and December 2017 follow-on public offerings, \$115.1 million in gross proceeds from the issuance of convertible preferred stock, \$18.8 million of upfront and milestone payments under our former collaboration with Alexion Pharma Holding, or Alexion, \$55.0 million in upfront and milestone payments under our existing collaboration with Roche, a \$40.0 million upfront payment under our existing collaboration with CStone, and \$10.0 million in gross proceeds from the debt financing.

Since inception, we have incurred significant operating losses. Our net losses were \$236.6 million, \$148.1 million and \$72.5 million for the years ended December 31, 2018, 2017 and 2016. As of December 31, 2018, we had an accumulated deficit of \$597.5 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 several years and for the foreseeable future. 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, if we obtain marketing approval for our drug candidates, we will incur significant sales, marketing and outsourced-manufacturing expenses. We have incurred and will continue to incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing 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 revenue.

To date, we have not generated any revenue from our most advanced drug candidates, avapritinib, BLU-667, BLU-554 and BLU-782. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to sell, avapritinib, BLU-667, BLU-554 or one of our other drug candidates. We do not expect to generate any revenue from the sale of avapritinib until 2020, assuming we are able to file for regulatory approval for avapritinib in the United States in the second quarter of 2019 and receive marketing approval by 2020. Our ability to generate 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;
- establish commercial manufacturing capabilities or make arrangements with third-party manufacturers for clinical supply and commercial manufacturing;
- commercialize our drug candidates, if approved, by developing a sales force or entering into additional collaborations with third parties; and
- achieve market acceptance of our drug candidates in the medical community and with third-party payors.

We expect to incur significant sales and marketing costs as we prepare to commercialize our drug candidates. 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 drug revenue, we will not become profitable and may be unable to continue operations without continued funding.

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

The development of pharmaceuticals is capital-intensive. We are currently advancing our most advanced drug candidates, avapritinib, BLU-667, BLU-554 and BLU-782, through clinical 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. In addition, depending on the status of regulatory approval or, if we obtain marketing approval for any of our drug candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Roche, CStone or other collaborators. We may also need to raise additional funds sooner if we choose to pursue additional indications or geographies for our drug candidates or otherwise expand more rapidly than we presently anticipate. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate certain of our research and development programs or future commercialization efforts.

As of December 31, 2018, we had cash, cash equivalents and investments of \$494.0 million. Based on our current plans, we believe our existing cash, cash equivalents and investments, excluding any potential option fees and milestone payments under our existing collaborations with Roche and CStone, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the second half of 2020. Our future capital requirements will depend on and could increase significantly as a result of many factors, including:

- the scope, progress, results and costs of drug discovery, pre-clinical development, laboratory testing and clinical trials for our drug candidates;

- the costs of securing and producing drug substance and drug product material for use in pre-clinical studies, clinical trials and for use as commercial supply;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our drug candidates;
- the success of our collaborations with Roche and CStone;
- the success of our current or future collaborations for companion diagnostic tests;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under our collaboration agreements with Roche or CStone or any collaboration agreements that we may enter into in the future;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other drug candidates and technologies;
- the costs of securing manufacturing arrangements for development activities and commercial production;
- the costs of establishing operations outside the United States; and
- the costs of establishing or contracting for sales, marketing and distribution capabilities if we obtain regulatory approvals to market our drug candidates.

Identifying potential drug candidates and conducting pre-clinical development and testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug candidates, if approved, may not achieve commercial success. Accordingly, we will need to continue to rely on additional financing to achieve our 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 our drug candidates. Dislocations in the financial markets have generally made equity and debt financing more difficult to obtain and may have a material adverse effect on our ability to meet our fundraising needs. 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. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborators or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies 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, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any drug candidate 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 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 and CStone, 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 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 candidates that we would otherwise prefer to develop and market ourselves.

**Risks Related to Drug Development and Regulatory Approval**

***We are very early in our development efforts with only four drug candidates in clinical development: avapritinib, BLU-667, BLU-554 and BLU-782. All of our other drug candidates are currently in pre-clinical or earlier stages of development. If we are unable to advance our other drug candidates to clinical development, obtain regulatory approval for our most advanced drug candidates or other drug candidates and ultimately commercialize our most advanced drug candidates or other drug candidates, or experience significant delays in doing so, our business will be materially harmed.***

We are very early in our development efforts with only four drug candidates in clinical development: avapritinib, BLU-667, BLU-554 and BLU-782. All of our other drug candidates are currently in pre-clinical or earlier stages of development. We have invested substantially all of our efforts and financial resources in the identification and pre-clinical development of kinase inhibitors, including the development of our drug candidates avapritinib, BLU-667, BLU-554 and BLU-782. Our ability to generate drug revenues, if ever, will depend heavily on the successful development and eventual commercialization of our drug candidates, which may never occur. We currently generate no revenues from sales of any drugs, and we do not expect to generate any revenue from the sale of avapritinib until 2020, assuming we are able to file for regulatory approval for avapritinib in the United States in the second quarter of 2019 and receive marketing approval by 2020. We may never be able to develop or commercialize a marketable drug. Each of our drug candidates will require additional pre-clinical or clinical development, management of clinical, pre-clinical and manufacturing activities, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenues from drug sales. 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, we may seek to develop companion diagnostic tests, which are assays or tests to identify an appropriate patient population. For example, we have entered into agreements with third parties to develop and commercialize companion diagnostics for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-554 in order to identify HCC patients with FGFR4 pathway activation and BLU-667 in order to identify NSCLC patients with RET fusions. Companion diagnostic tests are subject to regulation as medical devices and must themselves be approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our drug candidates. The success of our most advanced drug candidates and other drug candidates will depend on several factors, including the following:

- successful enrollment in, and completion of, clinical trials, including our current clinical trials for avapritinib, BLU-667, BLU-554 and BLU-782;

- successful completion of pre-clinical studies for our other drug candidates;
- approval of Investigational New Drug applications for future clinical trials for our other drug candidates;
- successful development of any companion diagnostic tests for use with our current or future drug candidates;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers for clinical supply and commercial manufacturing;
- obtaining and maintaining patent and trade secret protection or regulatory exclusivity for our drug candidates;
- launching commercial sales of our drug candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the 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 the 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 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.

***We do not know whether we will be able to develop any drugs of commercial value.***

Our scientific approach focuses on using our novel target discovery engine and our proprietary compound library to identify new kinase targets in disease indications. Our focus on using our novel target discovery engine to identify potential kinase targets in disease indications may not result in the discovery and development of commercially viable drugs for these diseases. The use of our proprietary compound library may not lead to the development of commercially viable drugs. Even if we are able to develop a drug candidate that successfully targets these kinases in pre-clinical studies, we may not succeed in demonstrating safety and efficacy of the drug candidate in clinical trials.

***Clinical drug development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our drug candidates.***

Our drug candidates avapritinib, BLU-667, BLU-554 and BLU-782 are in clinical development, and all of our other drug candidates are in pre-clinical development. The risk of failure for our drug candidates is high. It is impossible to predict when or if any of our drug candidates will prove effective and safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any drug candidate, we must complete pre-clinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our drug candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of pre-clinical development testing and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. Moreover, pre-clinical and clinical data are often

susceptible to varying interpretations and analyses, and many companies that have believed their drug candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval of their drug candidates. Our pre-clinical studies, current clinical trials and future clinical trials may not be successful.

Successful completion of our clinical trials is a prerequisite to submitting a new drug application, or NDA, to the FDA and a Marketing Authorization Application, or MAA, in the European Union for each drug candidate and, consequently, the ultimate approval and commercial marketing of avapritinib, BLU-667, BLU-554, BLU-782 and our other drug candidates. We do not know whether any of our clinical trials for our drug candidates will be completed on schedule, if at all.

We may experience delays in completing our pre-clinical studies and initiating or completing clinical trials, and we may experience numerous unforeseen events during, or as a result of, any current or future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our drug candidates, including:

- regulators or institutional review boards, or IRBs, or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trials of our drug candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional pre-clinical studies or clinical trials or we may decide to abandon drug development programs;
- patients treated with our drug candidates may develop mutations that confer resistance to treatment, which may limit the market opportunity for our drug candidates or prevent us from completing our clinical trials, obtaining regulatory approval for or commercializing our drug candidates;
- the number of patients required for clinical trials of our drug candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators or IRBs or ethics committees may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our drug candidates may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate;
- our drug candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or IRBs or ethics committees to suspend or terminate the trials, or reports may arise from pre-clinical or clinical testing of other cancer therapies that raise safety or efficacy concerns about our drug candidates; and
- the FDA or other regulatory authorities may require us to submit additional data or impose other requirements before permitting us to initiate a clinical trial.

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our drug candidates. Further, the FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or the FDA may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials.

If we are required to conduct additional clinical trials or other testing of our drug candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our drug candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our drug candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- be subject to post-marketing testing requirements; or
- have the drug removed from the market after obtaining marketing approval.

Our drug development costs will also increase if we experience delays in testing or regulatory approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant pre-clinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our drug candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our drug candidates and may harm our business and results of operations. Any delays in our pre-clinical or future clinical development programs may harm our business, financial condition and prospects significantly.

***We may choose not to develop a potential drug candidate, or we may suspend, deprioritize or terminate one or more discovery programs or pre-clinical drug candidates or programs.***

At any time and for any reason, we may determine that one or more of our discovery programs or pre-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 pre-clinical drug candidates or programs. For example, we have previously determined to suspend our discovery program for inhibitors of neurotrophic tyrosine receptor kinase, or NTRK, and predicted NTRK resistant mutants, and to deprioritize our discovery program targeting protein kinase cAMP-activated catalytic subunit alpha fusions for the treatment of fibrolamellar carcinoma. 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.

***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 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 United States. In particular, because we are focused on diseases in genomically defined patient populations, our ability to enroll eligible patients may be limited or may result in slower enrollment than we anticipate. In addition, some of our competitors have ongoing clinical trials for drug candidates that treat the same indications as

our drug candidates, 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.

***Because the target patient populations for our drug candidates are relatively small, it may be difficult to successfully identify patients, could delay enrollment for our trials. If the market opportunities for our drug candidates are smaller than we believe they are, our product revenues may be adversely affected, and our business may suffer.***

We focus our research and product development on treatments for cancer and rare genetic diseases, including genomically defined cancer and diseases driven by abnormal kinase activation. Because the target patient populations for our drug candidates are relatively small, it may be difficult to successfully identify patients. We have entered into agreements with third parties to develop a companion diagnostic test for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-554 in order to identify HCC patients with FGFR4 pathway activation and BLU-667 in order to identify NSCLC patients with RET fusions. We plan to engage a third party to develop a companion diagnostic test for use in our planned COMPASS-2L trial, and we may engage third parties to develop companion diagnostic tests for use in some of our other current or future clinical trials. However, third parties may not be successful in developing such companion diagnostic tests, furthering the difficulty in identifying patients for our clinical trials.

Our inability 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. In addition, our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our drug candidates, are based on estimates. These estimates may prove to be incorrect, and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our drug candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, prospects and ability to achieve or sustain profitability.

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

Our drug candidates and any related companion diagnostic tests, including the companion diagnostic tests that we are developing for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-554 in order to identify HCC patients with FGFR4 pathway activation and BLU-667 in order to identify NSCLC patients with RET fusions, 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 United States 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 approval for any related companion diagnostic tests, including the companion diagnostic tests that we are developing for avapritinib, BLU-667 and BLU-554. We have not received approval to market any of our drug candidates or related companion diagnostic tests from regulatory authorities in any jurisdiction, and it is possible that none of our current or future drug candidates or related companion diagnostic tests will ever obtain regulatory approval. We have only limited experience in filing and supporting the applications necessary to gain regulatory approvals and expect to rely on third-party CROs and/or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive pre-clinical 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. 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 United States 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 pre-clinical, clinical or other studies. 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 pre-clinical 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 United States 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; and
- 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.

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 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 related companion diagnostic tests, the commercial prospects for our drug candidates may be harmed and our ability to generate revenues will be materially impaired.

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

Undesirable side effects caused by our drug candidates could cause us to interrupt, delay or halt pre-clinical 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 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 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 the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, our drug candidates could cause undesirable side effects in clinical trials related to on-target toxicity. For example, the FGF19/FGFR4 signaling axis has been shown to play a role in the regulation of de novo bile acid synthesis. Modulation of this signaling axis by treatment with a small molecule FGFR4 inhibitor could lead to the clinical symptoms that were observed with administration of an FGF19 antibody. If on-target toxicity is observed, or if our 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 drug candidates may only be uncovered with a significantly larger number of patients exposed to the drug candidate. If our drug candidates receive marketing approval and we or others identify undesirable side effects caused by such drug candidates (or any other similar drugs) after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw or limit their approval of such drug candidates;
- 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 candidates are distributed or administered, conduct additional clinical trials or change the labeling of the drug candidates;
- 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 candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our 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 drug candidates and could substantially increase the costs of commercializing our drug candidates, if approved, and significantly impact our ability to successfully commercialize our drug candidates and generate revenues.

***A breakthrough therapy designation by the FDA for our drug candidates, including avapritinib, 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.***

In June 2017, the FDA granted breakthrough therapy designation to avapritinib for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation, and in October 2018, the FDA granted breakthrough therapy designation to avapritinib for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia. In December 2018, the FDA granted breakthrough therapy designation to BLU-667 for the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments. We may also seek breakthrough therapy designation for some of our other 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.

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.

***A fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.***

The FDA has granted fast track designation to avapritinib for (i) the treatment of patients with unresectable or metastatic GIST that progressed following treatment with imatinib and a second TKI and (ii) the treatment of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior therapy, and the FDA has granted fast track designation to BLU-782 for the treatment of FOP. We may also seek fast track designation for some of our other drug candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the drug sponsor may apply for fast track designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular drug candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even though

we have received fast track designation for avapritinib for treatment of patients with unresectable or metastatic GIST that progressed following treatment with imatinib and a second tyrosine kinase inhibitor and for the treatment of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior therapy, or even if we receive fast track designation for our other drug candidates, we may not experience a faster development process, review or approval. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

***While we have received orphan drug designation for our most advanced drug candidates, avapritinib, BLU-667 and BLU-554, for specified indications, we may seek orphan drug designation for some of our other drug candidates. However, 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 BLU-554 for the treatment of HCC and to BLU-667 for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC. 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 United States 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 United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers.

Similarly, in the European Union, the European Commission grants medicinal product designation after receiving the opinion of the EMA's 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 5 in 10,000 persons in the European Union and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product 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 European Union would be sufficient to justify the necessary investment in developing the drug. In the European Union, 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 United States and ten years in the European Union. The European Union 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. 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 United States 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 seek orphan drug designation for our other drug candidates in addition to avapritinib for the treatment of GIST and the treatment of mastocytosis, BLU-554 for the treatment of HCC and BLU-667 for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC, 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.

***Even if we receive regulatory approval for any of our drug candidates, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. In addition, our drug candidates, if approved, 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.***

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, or voluntary 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.

***We may not be successful in our efforts to use and expand our discovery platform to build a 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. Even if we are successful in continuing to build 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 receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize drug candidates based upon our approach, 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 financial and managerial 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.

### **Risks Related to Commercialization**

***The incidence and prevalence for target patient populations of our drug candidates have not been established with precision. If the market opportunities for our 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, possibly materially.***

The precise incidence and/or prevalence for GIST, SM, RET-altered NSCLC and MTC, HCC and FOP are unknown. Our projections of the number of people who have these diseases, the frequency of the genetic alterations targeted by our drug candidates and the subset of people with these diseases who have the potential to benefit from treatment with our drug candidates are based on estimates. We estimate that in the United States, France, Germany, Italy, Spain, the United Kingdom and Japan, or the Major Markets, there are approximately: 20,700 patients with SM, including 2,600 patients with advanced SM and 18,100 patients with ISM and SSM (regardless of severity of symptoms); 500 first-line patients with PDGFRA D842V mutant GIST (including resectable, metastatic and unresectable GIST); 7,500 second-line patients with GIST, including approximately 75%-80% of second-line patients with GIST who do not have a KIT V654A or T670I mutation; 7,400 third-line and later patients with GIST (regardless of alteration); 8,900 first- and second-line patients with RET-altered NSCLC; 1,300 patients with MTC (regardless of line of therapy or alteration); 25,900 first- and second-line patients with FGFR4-activated HCC; and 1,100 patients with FOP.

The total addressable market opportunity for avapritinib for the treatment of patients with GIST and SM, BLU-667 for the treatment of patients with RET-altered NSCLC and MTC, BLU-554 for the treatment of patients with advanced HCC and BLU-782 for the treatment of patients with FOP will ultimately depend upon, among other things, the diagnosis criteria included in the final label for each of avapritinib, BLU-667, BLU-554 and BLU-782, if our drug candidates are approved for sale for these indications, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients in 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 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 discovering, developing or commercializing 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 current drug candidates, and we will face competition with respect to any 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. If avapritinib receives marketing approval for advanced SM, it will face competition from Novartis AG's midostaurin, a multi-kinase inhibitor with KIT D816V inhibitory activity that was approved in April 2017 by the FDA for the treatment of advanced SM. If avapritinib receives marketing approval for third line advanced GIST, it will face competition from Bayer AG's regorafenib, and if avapritinib receives marketing approval for second line advanced GIST, it will face competition from Pfizer Inc.'s sunitinib. In addition, if avapritinib receives marketing approval for advanced SM, GIST and/or for GIST patients with the PDGFRA D842V

mutation, it may face competition from other drug candidates in development for these indications, including drug candidates in development by AB Science S.A., Allakos Inc., ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AROG Pharmaceuticals, Inc., Celldex Therapeutics, Inc., and Deciphera Pharmaceuticals, LLC. If BLU-667 receives marketing approval for patients with RET-driven cancers, it may face competition from other drug candidates in development, including drug candidates in development by ARIAD Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, AstraZeneca plc, Boston Pharmaceuticals, Inc., Eisai Inc., Exelixis, Inc., GlaxoSmithKline plc, Loxo Oncology, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Mirati Therapeutics, Inc., Novartis AG, Pfizer Inc. and Roche, as well as several approved multi-kinase inhibitors with RET activity being evaluated in clinical trials, including alectinib, apatinib, cabozantinib, dovitinib, lenvatinib, ponatinib, sorafenib, sunitinib and vandetinib.

If BLU-554 receives marketing approval for patients with FGFR4-activated HCC, it will face competition from Bristol-Myers Squibb Company's nivolumab and Merck & Co., Inc.'s pembrolizumab, immune checkpoint inhibitors approved by the FDA for the treatment of HCC, as well as sorafenib, cabozantinib, regorafenib and lenvatinib, multi-kinase inhibitors approved for the treatment of HCC. In addition, BLU-554 may face competition from other drug candidates in development by Abbisko Therapeutics Co., Ltd, AstraZeneca plc, Bayer AG, Celgene Corporation, Eisai Inc., H3 Biomedicine Inc., Incyte Corporation, Johnson & Johnson, Novartis AG, Sanofi S.A., Taiho Pharmaceutical Co., Ltd., U3 Pharma GmbH, a wholly-owned subsidiary of Daiichi Sankyo Company, Limited, and Xoma Ltd. If BLU-782 receives marketing approval for FOP, it may face competition from drug candidates in development by BioCryst Pharmaceuticals, Inc., Clementia Pharmaceuticals Inc., La Jolla Pharmaceutical Company and Regeneron Pharmaceuticals, Inc.

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, pre-clinical 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 drug candidates that we may develop.***

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

- decreased demand for any drug candidates that we may develop;
- 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 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 will need to increase our insurance coverage when we begin later-stage clinical trials and if we successfully commercialize any drug candidate. 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.

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

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our 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 commercialize companion diagnostic tests with third parties for avapritinib in order to identify GIST patients with the PDGFRA D842V mutation, BLU-554 in order to identify HCC patients with FGFR4 pathway activation and BLU-667 in order to identify NSCLC patients with RET fusions, and we expect to develop a companion diagnostic test with a third party for avapritinib for our planned COMPASS-2L trial in order to select patients with PDGFRA- and KIT-driven second-line GIST who do not test positive for the KIT V654A or T670I mutations. However, we have not yet initiated commercialization of these companion diagnostic tests or development and commercialization of companion diagnostic tests for any of our other programs. We have little experience in the development and commercialization of companion diagnostic tests and may not be successful in developing and commercializing appropriate companion diagnostic tests to pair with any of our drug candidates that receive marketing approval. Companion diagnostic tests are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization. Given our limited experience in developing and commercializing companion diagnostic tests, we are relying on third parties to design, manufacture, obtain regulatory approval for and commercialize the companion diagnostic tests for avapritinib, BLU-667 and BLU-554, and we expect to rely in whole or in part on third parties to design, manufacture, obtain regulatory approval for and commercialize any other companion diagnostic tests for our drug candidates. We and our collaborators may encounter difficulties in developing and obtaining 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 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 approval of the companion diagnostic tests could delay or prevent 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 drug candidates, or experience delays in doing so:

- the development of our 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; and
- we may not realize the full commercial potential of any 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 would be harmed, possibly materially.

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 drug candidates, if approved. 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 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 drug candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our drug candidates.

***Even if we are able to commercialize any drug candidates, such drugs 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 drug candidates successfully also will depend in part on the extent to which coverage and reimbursement for these drug candidates and related treatments will be available from government authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and 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.

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 United States. 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 United States. 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.***

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 Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the Affordable Care Act, was passed, which substantially changes the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses 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, increases the 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 a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% 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 United States since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2027 unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, the Middle Class Tax Relief and Job Creation Act of 2012 required that CMS reduce the Medicare clinical laboratory fee schedule by 2% in 2013, which served as a base for 2014 and subsequent years. In addition, effective January 1, 2014, CMS also began bundling the Medicare payments for certain laboratory tests ordered while a patient received services in a hospital outpatient setting. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our drug candidates or companion diagnostic tests or additional pricing pressures.

Since its enactment, some of the provisions of the Affordable Care Act have yet to be fully implemented, while certain provisions have been subject to judicial, congressional, and executive challenges. In 2012, the U.S. Supreme Court upheld certain key aspects of the legislation, including a tax-based shared responsibility payment imposed on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly the requirement that all individuals maintain health insurance coverage or pay a penalty, referred to as the "individual mandate." Though Congress has not passed repeal legislation to date, the 2017 Tax Reform Act included a provision which repealed the individual mandate effective January 1, 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the Affordable Care Act is an essential and inseparable feature of the Affordable Care Act, and therefore because the mandate was repealed as part of the 2017 Tax Reform Act, the remaining provisions of the Affordable Care Act are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the Affordable Care Act will impact the Affordable Care Act and our business.

Further, on January 20, 2017, U.S. President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices.

On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the Affordable Care Act. 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. In addition, the Centers for Medicare & Medicaid Services, the agency responsible for administering the Medicare program, or CMS, recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the health benefits required under the Affordable Care Act for plans sold through these marketplaces. For example, on November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule would allow Medicare Advantage plans to use pre-authorization and step therapy for six protected classes of drugs, with certain exceptions; permit plans to implement pre-authorization and step therapy in Medicare Part B drugs; change the definition of “negotiated prices”; and add a new definition of “price concession.” It is unclear whether these proposed changes will be accepted, and if so, what effect such changes will have on our business. Congress will likely continue to consider subsequent legislation and further action to repeal, replace or modify the Affordable Care Act. It is unclear what impact any changes to the Affordable Care Act will have on the availability of healthcare and containing or lowering the cost of healthcare. We plan to continue to evaluate the effect that the Affordable Care Act and its possible repeal and replacement may have on our business.

Healthcare reforms stemming from the repeal of, and potential replacement for, the Affordable Care Act may result in more rigorous coverage criteria and lower reimbursement among regulated third-party payors, and in additional downward pressure on the prices that we receive for sales of our products, if approved. Any reduction in reimbursement from Medicare or other government-funded federal programs, including the Veterans Health Administration, or state healthcare programs could lead to a similar reduction in payments from private commercial payors. The implementation of cost containment measures or other healthcare reforms may thus prevent us from being able to generate revenue or attain profitability.

Beyond challenges to the Affordable Care Act, other legislative measures have also been enacted that may impose additional pricing and product development pressures on our business. For example, on May 30, 2018, the Right to Try Act, was signed into law. Among other things, this law 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 drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy. 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 products, once approved, or additional pricing pressures.

The delivery of healthcare in the European Union, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize any products for which we obtain marketing approval.

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 potential commercialization of our products.

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

We do not currently have a sales or marketing infrastructure and have limited experience in the sale, marketing or distribution of drugs. To achieve commercial success for any approved drug candidate for which we retain sales and marketing responsibilities, we must build our sales, marketing, managerial, and other non-technical capabilities or make arrangements with third parties to perform these services. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, some of our 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 recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future drugs;
- the lack of complementary drugs to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, 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 drug candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our drug candidates or may be unable to do so on terms that are favorable to us. 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 drug candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our drug candidates. Further, our business, results of operations, financial condition and prospects will be materially adversely affected.

***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.***

Although we do not currently have any drugs on the market, once we begin commercializing our drug candidates, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any drug candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to

broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our drug candidates for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid. 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;
- the federal False Claims Act imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; 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;
- the federal physician payment transparency requirements, sometimes referred to as the “Sunshine Act” under the Affordable Care Act require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value and the ownership and investment interests of such physicians and their immediate family members;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and its implementing regulations, which also imposes obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouses as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for 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);
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; and some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures, and state laws governing the privacy and security of health information in certain

circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

On January 31, 2019, the Department of Health and Human Services, or HHS, and HHS Office of Inspector General, or OIG, proposed an amendment to one of the existing anti-kickback safe harbors (42 C.F.R. 1001.952(h)) that would prohibit certain pharmaceutical manufacturers from offering rebates to pharmacy benefit managers in the Medicare Part D and Medicaid managed care programs. The proposed amendment would remove protection for "discounts" from anti-kickback enforcement action and would include criminal and civil penalties for knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or reward the referral of business reimbursable under federal health care programs. At the same time, HHS also proposed to create a new safe harbor to protect point-of-sale discounts that drug manufacturers provide directly to patients and add another safe harbor to protect certain administrative fees paid by manufacturers to pharmacy benefit managers. If this proposal is adopted, in whole or in part, it could affect the pricing and reimbursement for any products for which we receive approval in the future.

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 our 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, and we may never receive such regulatory approval for any of our drug candidates. 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 and commercial sales, pricing and distribution of our drug candidates, and we cannot predict success in these jurisdictions. If we 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;
- 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 United States tend to impose strict price controls, which may adversely affect our revenues, if any.***

In some countries, particularly countries in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a 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. In addition, in 2016, the United Kingdom referendum on its membership in the European Union resulted in a majority of United Kingdom voters voting to exit the European Union, often referred to as Brexit. Brexit has already and may continue to adversely affect European and/or worldwide regulatory conditions. Brexit could lead to legal uncertainty and potentially divergent national laws and regulations, including those related to the pricing of prescription pharmaceuticals, as the United Kingdom determines which European Union laws to replicate or replace. If the United Kingdom were to significantly alter its regulations affecting the pricing of prescription pharmaceuticals, we could face significant new costs. As a result, Brexit could impair our ability to transact business in the European Union and the United Kingdom.

***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 Dependence on Third Parties**

***We may seek to establish additional collaborations, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.***

Our drug development programs and the potential commercialization of our drug candidates will require substantial additional cash to fund expenses. For some of our drug candidates, we may decide to collaborate with additional pharmaceutical and biotechnology companies for the development and potential commercialization of those drug candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject drug candidate, the costs and complexities of manufacturing and delivering such drug candidate to patients, the potential of competing drugs, the

existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative drug candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our drug candidate. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us.

We may also be restricted under our collaboration agreements with Roche and CStone from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

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

In addition, our collaborations with Roche and CStone, as well as any future collaborations that we enter into, may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. 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. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority. Collaborations 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 agreements with Roche and CStone or any future collaboration agreement could adversely affect us financially or harm our business reputation.

***We rely on third parties to conduct our clinical trials for our drug candidates. 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 drug candidates. We rely heavily on these parties for execution of clinical trials for our 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 the clinical trials for our drug candidates, CROs will conduct all of the 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.

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 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 candidates. As a result, we believe that our financial results and the commercial prospects for our drug candidates in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

***We contract with third parties for the manufacture of our drug candidates for pre-clinical development and clinical trials, and we expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs 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, on third parties for the manufacture of our drug candidates for pre-clinical development and clinical testing, as well as for the commercial manufacture of our drugs if any of our drug candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our drug candidates or drugs 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 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 drug candidates. 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 drug candidates or if it withdraws any such approval in the future, we may 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. 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 drug candidates.

We do not have any long-term supply agreements with our contract manufacturers, and we purchase our required drug supply, including the drug product and drug substance used in our most advanced drug candidates, on a purchase order basis. 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.

Our drug candidates and any drugs that we may develop may compete with other drug candidates and approved drugs 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.

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 bulk drug substances. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. Although we believe that there are several potential alternative manufacturers who could manufacture our 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 drug candidates or drugs could result in significant delays or gaps in availability of such drug candidates or drugs 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 active pharmaceutical ingredient, or API, drug substance and drug product used in our most advanced drug candidates 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 most advanced drug candidates are currently supplied to us 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 our most advanced drug candidates, 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, it could significantly and adversely affect our business, the supply of our drug candidates and our financial condition.

For all of our drug candidates, we intend 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, however, 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.

Establishing additional or replacement suppliers for the API, drug substance and drug product used in our drug candidates, 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, 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.

### **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 United States and other countries for our lead drug candidate, avapritinib, as well as our other most advanced drug candidates, BLU-667, BLU-554 and BLU-782, 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 United States and abroad related to our proprietary compounds, technology, 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 patents and patent applications that relate to avapritinib, BLU-667, BLU-554 and BLU-782 as composition of matter. We also own applications relating to composition of matter for KIT inhibitors with multiple compound families, composition of matter for FGFR4 inhibitors with multiple compound families, composition of matter for inhibitors of RET, including predicted RET resistance mutations, with multiple compound families, and composition of matter for inhibitors of ALK2, with multiple compound families, as well as methods of use for these novel compounds. The issued patent directed to avapritinib composition of matter has a statutory expiration date in 2034, the issued patent directed to BLU-554 composition of matter has a statutory expiration date in 2034 and the issued patent directed to BLU-667 composition of matter has a statutory expiration date in 2036.

As of February 15, 2019, we owned nine issued U.S. patents, four issued foreign patents, including one European patent validated in 38 countries, three pending U.S. non-provisional patent applications, two pending U.S. provisional patent applications, 40 pending foreign patent applications and one pending Patent Cooperation Treaty, or PCT, international patent application directed to our KIT program, including avapritinib. Our foreign patent filings are in a number of jurisdictions, including Australia, Argentina, Brazil, Bolivia, Canada, China, the European Union, Hong Kong, Israel, India, Japan, Lebanon, Mexico, New Zealand, Pakistan, Paraguay, Philippines, Russia, Singapore, South Africa, South Korea, Taiwan, Uruguay and Venezuela. Any U.S. or ex-U.S. patents issuing from the pending applications covering avapritinib will have a statutory expiration date between October 2034 and January 2040. Patent term adjustments or patent term extensions could result in later expiration dates.

As of February 15, 2019, we owned four issued U.S. patents, three pending U.S. non-provisional patent applications, one pending PCT international application, 28 pending foreign patent applications and six pending U.S. provisional patent applications directed to our RET program, including BLU-667. Our foreign patent filings are in a number of jurisdictions, including Argentina, Australia, Brazil, Canada, China, Chile, Ecuador, Eurasia, the European Union, Israel, India, Japan, Lebanon, Malaysia, Mexico, New Zealand, Philippines, Saudi Arabia, Singapore, South Africa, South Korea, Taiwan, Thailand, the United Arab Emirates and Uruguay. Any U.S. or ex-U.S. patent issuing from

the pending applications covering BLU-667 will have a statutory expiration date between November 2036 and August 2039. Patent term adjustments or patent term extensions could result in later expiration dates.

As of February 15, 2019, we owned seven issued U.S. patents, two pending U.S. non-provisional patent applications, eight issued foreign patents, 39 pending foreign patent applications and one pending PCT international patent application directed to our FGFR4 program, including BLU-554. Our foreign patent filings are in a number of jurisdictions, including Argentina, Australia, Bolivia, Brazil, Canada, China, Egypt, the European Union, Hong Kong, Israel, India, Indonesia, Japan, South Korea, Lebanon, Mexico, New Zealand, Pakistan, Paraguay, Philippines, Russia, Singapore, South Africa, Taiwan, Thailand, Uruguay, Venezuela and Vietnam. Any U.S. or ex-U.S. patent issuing from the pending applications covering BLU-554 will have a statutory expiration date between July 2033 and September 2037. Patent term adjustments or patent term extensions could result in later expiration dates.

As of February 15, 2019, we owned one pending U.S. non-provisional patent application, one pending PCT international application and 15 pending foreign patent applications directed to our ALK2 program, including BLU-782. Our foreign patent filings are in a number of jurisdictions, including Australia, Brazil, Canada, China, Chile, the European Union, Israel, Japan, South Korea, Mexico, New Zealand, Eurasia and South Africa. Any U.S. or ex-U.S. patent issuing from pending applications covering BLU-782 will have statutory expiration dates of April 2037 or October 2038. Patent term adjustments or patent term extensions could result in later expiration dates.

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 February 15, 2019, we owned ten pending U.S. non-provisional patent applications, nine pending European Union patent applications and one issued European patent directed to this technology. 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 2039.

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 our 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 avapritinib, BLU-667, BLU-554, BLU-782 or our other drug candidates. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Furthermore, patents have a limited lifespan. In the United States, 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 patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing drugs similar or identical to our drug candidates, including generic versions of such drugs.

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 United States 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 BLU-554 or generic method of treatment claims that may cover BLU-667. If the claims of any of these third-party patents are asserted against us, we do not believe BLU-554, BLU-667 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 United States and

abroad could uphold the validity of any such patents. If we were to challenge the validity of any issued United States patent in court, we would need to overcome a statutory presumption of validity that attaches to every United States 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. Further, with respect to some of the pending patent applications covering our drug candidates, prosecution has yet to commence. 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, in some circumstances, 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 United States 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 or consultants 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 and drug candidates. Such challenges may also result in our inability to manufacture or commercialize our drug candidates 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 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 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 drug candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our drug candidates 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 drug candidates 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 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 kinase inhibitors. 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 BLU-554 or generic method of treatment claims that may cover BLU-667. If the claims of any of these third-party patents are asserted against us, we do not believe BLU-554, BLU-667 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 United States and abroad could uphold the validity of any such patents. If we were to challenge the validity of any issued United States patent in court, we would need to overcome a statutory presumption of validity that attaches to every United States 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 drug candidates. If a patent holder believes our drug or drug candidate infringes on its patent, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect.

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 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 drug candidates 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 United States, 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 one of our drug candidates, we would lose at least part, and perhaps all, of the patent protection covering such 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 or procedures, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our 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 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 United States. 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 United States. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drugs and, further, may export otherwise infringing drugs to 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 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 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 United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our 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 United States 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 United States 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 United States 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 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 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 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 drug candidates. 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 drug candidates, which would have an adverse effect on our business, results of operations and financial condition.

#### **Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business**

***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, business development, financial and legal expertise of Jeffrey W. Albers, our President and Chief Executive Officer, Anthony L. Boral, our Chief Medical Officer, Marion Dorsch, our Chief Scientific Officer, Kathryn Haviland, our Chief Operating Officer, Michael Landsittel, our Chief Financial Officer, Tracey McCain, our Chief Legal and Compliance Officer, Christopher Murray, our Senior Vice President of Technical Operations, and Christina Rossi, our Chief Commercial Officer, 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. 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, manufacturing and sales and marketing personnel will be 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 February 15, 2019, we had 217 full-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 global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the global financial crisis, 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.

Following its June 23, 2016 vote to leave the European Union, on March 29, 2017, the United Kingdom invoked Article 50 of the Lisbon Treaty and formally began the process of exiting the European Union. Although Brexit has already and may continue to adversely affect European and/or worldwide economic or market, political or regulatory conditions and may contribute to instability in the global financial markets, political institutions and regulatory agencies, the resulting immediate changes in foreign currency exchange rates have had a limited overall impact due to natural hedging. Given the lack of comparable precedent, it is unclear what financial, trade and legal implications the withdrawal of the United Kingdom from the European Union would have and how such withdrawal would affect us. The long-term impact of Brexit, including on our business and our industry, will depend on the terms that are negotiated in relation to the United Kingdom's future relationship with the European Union, and we are closely monitoring the Brexit developments in order to determine, quantify and proactively address changes as they become clear.

For example, Brexit could result in the United Kingdom or the European Union significantly altering its regulations affecting the clearance or approval of our product candidates that are developed in the United Kingdom. Any new regulations could add time and expense to the conduct of our business, as well as the process by which our products receive regulatory approval in the United Kingdom, the European Union and elsewhere. In addition, the announcement of Brexit and the withdrawal of the United Kingdom from the European Union have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets, and may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Any of these effects of Brexit, among others, could adversely affect our business, our results of operations, liquidity and financial condition.

***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 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 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 drug candidates' development programs and significant reputational, financial, legal, regulatory, business or operational harm. For example, the loss of clinical trial data for our 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 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.

***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 United States, 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. On May 25, 2018, the European General Data Protection Regulation 2016/679, or GDPR, took effect. The GDPR applies to any company established in the European Union as well as any company outside the European Union that collects or otherwise processes personal data in connection with the offering goods or services to individuals in the European Union 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's 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 European Union. If enacted, we will be subject to the EU ePrivacy Regulation, which is a proposed regulation of privacy and electronic communications. In addition, we will be subject to the California Consumer Privacy Act, which takes effect January 1, 2020 and will impose 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. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could 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 United States 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 pre-clinical 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 businesses or drugs, or form strategic alliances, in the future, and we may not realize the benefits of such acquisitions.***

We may acquire additional businesses or drugs, form strategic alliances or create joint ventures with third parties 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 resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, 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. In recent years, many such changes have been made and changes are likely to continue to occur in the future. We cannot predict whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or decided, which could result in an increase in our, or our stockholders', tax liability or require changes in the manner in which we operate in order to minimize increases in our tax liability.

On December 22, 2017, the Tax Cuts and Jobs Act, or TCJA, was enacted. The TCJA significantly reforms the Internal Revenue Code of 1986, as amended. The TCJA, among other things, includes changes to U.S. federal tax rates, imposes significant additional limitations on the deductibility of interest and net operating loss carryforwards and allows for the expensing of capital expenditures. Our net deferred tax assets and liabilities were revalued as of December 31, 2017 at the newly enacted U.S. corporate rate, and the impact was recognized in our tax expense in the year of enactment but was offset by a corresponding reduction to the valuation allowance. We continue to examine the impact this tax reform legislation may have on our business. The impact of this tax reform is uncertain and could be adverse.

### **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. In addition, the stock market in general, and Nasdaq listed and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. For example, our stock traded within a range of a high price of \$109.00 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, 2019. As a result of this volatility, our stockholders could incur substantial losses. In addition, the market price for our common stock may be influenced by many factors, including:

- 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 United States 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;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

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.

***An active trading market for our common stock may not be sustained, and investors may not be able to resell their shares at or above the price they paid.***

Although we have listed our common stock on The Nasdaq Global Select Market, an active trading market for our shares may not be sustained. In the absence of an active trading market for our common stock, investors may not be able to sell their common stock at or above the price at which they acquired their shares or at the time that they would like to sell. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

***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.

***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 increased 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, 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, 2018, we had federal net operating loss carryforwards of approximately \$464.9 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 carryforwards to reduce our taxable income in any year by more than 80%, and we may not carry back any net operating losses to prior years. These new rules apply regardless of the occurrence of an ownership change.

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

None.

#### **Item 2. Properties.**

Our headquarters are located at 45 Sidney Street in Cambridge, Massachusetts where we occupy approximately 99,833 rentable square feet of office and laboratory space under a lease that commenced on October 1, 2017 and will expire on November 30, 2029. On September 19, 2018, we entered into an amendment to the lease agreement to expand the rentable square footage from approximately 99,833 square feet to approximately 139,216 square feet. The initial term of the lease with respect to the expansion premises will commence on March 1, 2019 and will expire on November 30, 2029, unless terminated sooner. Pursuant to the lease amendment, the date on which we will become responsible for paying rent with respect to the expansion space will be the earlier of (i) the date upon which we first occupy the expansion premises for business purposes or (ii) July 1, 2019. We currently anticipate the rent commencement date for the expansion premises will be approximately July 1, 2019.

We also lease our former corporate headquarters at 38 Sidney Street in Cambridge, Massachusetts under a lease that will expire on October 31, 2022. The lease agreement provides us with an option to extend the lease for five additional years. In the first quarter of 2018, we fully subleased these premises through October 31, 2020. The sublessee has the option to extend the sublease through October 31, 2022, subject to specified exceptions under the sublease agreement.

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, 2019, there were approximately 16 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

#### Dividends

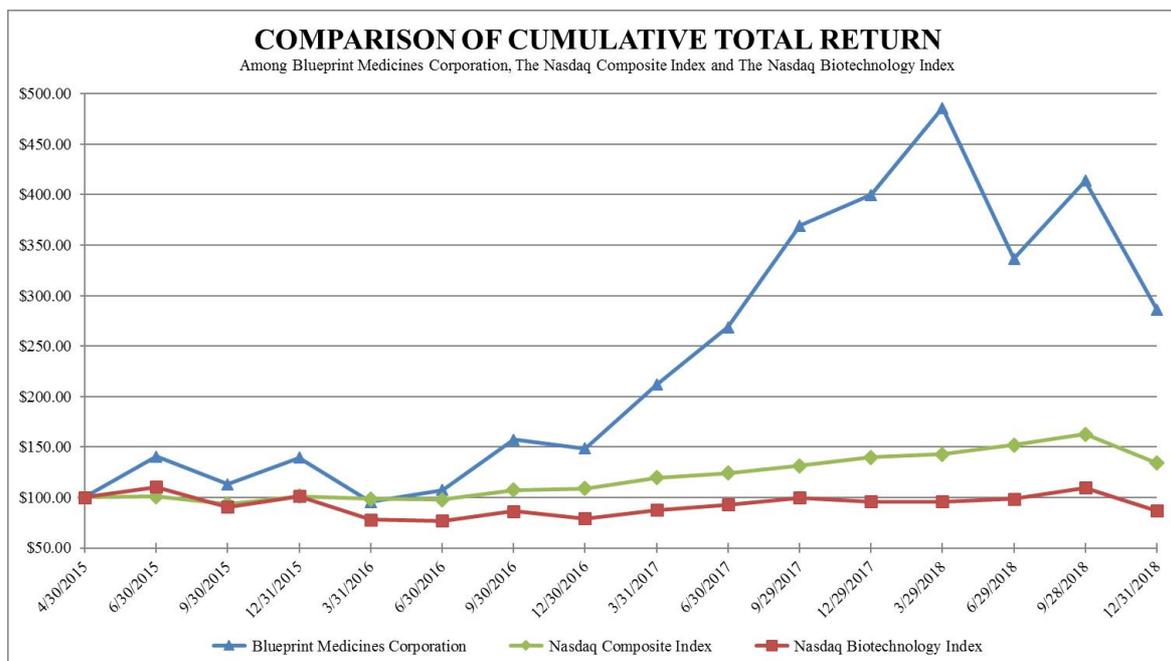
We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination 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 April 30, 2015 (the first date that shares of our common stock were publicly traded) through December 31, 2018. The comparison assumes \$100 was invested in our common stock and in each of the foregoing indices after the market closed on April 30, 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.



**Item 6. Selected Financial Data.**

You should read the following selected consolidated financial data together with our financial statements and the related notes appearing at the end of this Annual Report on Form 10-K and Item 7 “Management’s Discussion and Analysis of Financial Condition and Results of Operations” section of this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the years ended December 31, 2018, 2017 and 2016 and the consolidated balance sheet data as of December 31, 2018 and 2017 from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the year ended December 31, 2015 and 2014 and the consolidated balance sheet data as of December 31, 2016, 2015 and 2014 from our audited consolidated financial statements and related notes not included in this Annual Report on Form 10-K. The selected historical financial information in this section is not intended to replace our financial statements and the related notes thereto. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Year Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except per share data)				
<b>Statements of Operations Data:</b>					
Collaboration revenue	\$ 44,521	\$ 21,426	\$ 27,772	\$ 11,400	\$ —
Operating expenses:					
Research and development	243,621	144,687	81,131	48,588	31,844
General and administrative	47,928	27,986	19,218	14,456	7,890
Total operating expenses	291,549	172,673	100,349	63,044	39,734
Other income (expense):					
Other income (expense), net	10,459	3,349	551	(429)	(98)
Interest expense	(73)	(221)	(469)	(696)	(453)
Total other income (expense)	10,386	3,128	82	(1,125)	(551)
Net loss	\$(236,642)	\$ (148,119)	\$ (72,495)	\$ (52,769)	\$ (40,285)
Convertible preferred stock dividends	—	—	—	(3,153)	(5,765)

Net loss applicable to common stockholders	\$ (236,642)	\$ (148,119)	\$ (72,495)	\$ (55,922)	\$ (46,050)
Net loss per share applicable to common stockholders — basic and diluted(1)	\$ (5.39)	\$ (3.92)	\$ (2.64)	\$ (3.07)	\$ (32.41)
Weighted-average number of common shares used in net loss per share applicable to common stockholders — basic and diluted(1)	43,867	37,793	27,492	18,236	1,421

- (1) See Note 11, “Net Loss per Share” in the accompanying notes to our audited consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for further details on the calculation of basic and diluted net loss per share applicable to common stockholders.

	As of December 31,				
	2018	2017	2016	2015 (1)	2014
(in thousands)					
<b>Balance Sheet Data:</b>					
Cash and cash equivalents	\$ 68,064	\$ 400,304	\$ 52,069	\$ 162,707	\$ 47,240
Investments	425,948	273,052	216,149	—	—
Working capital(2)	439,464	642,615	191,913	151,776	41,510
Total assets	540,124	715,737	282,795	178,898	49,925
Deferred revenue	46,167	35,373	47,235	13,640	—
Term loan payable	—	1,518	4,069	7,338	9,042
Warrant liability	—	—	—	—	365
Convertible preferred stock	—	—	—	—	114,811
Total stockholders’ equity (deficit)	419,009	623,970	213,078	143,979	(79,382)

- (1) Upon the closing of our IPO in May 2015, all outstanding shares of our convertible preferred stock were converted into 15,467,479 shares of common stock, and warrants exercisable for convertible preferred stock were automatically converted into warrants exercisable for 42,423 shares of common stock.
- (2) We define working capital as current assets less current liabilities.

## 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.*

### Overview

We are a precision therapy company focused on genomically defined cancers, rare diseases and cancer immunotherapy. Our approach is to leverage our novel target discovery engine to systematically and reproducibly identify kinases that are drivers of diseases and to craft highly selective and potent drug candidates that may provide significant and durable clinical responses for patients without adequate treatment options. This integrated biology and chemistry approach enables us to identify, characterize and design drug candidates to inhibit novel kinase targets that have been difficult to selectively inhibit. We believe that our uniquely targeted, scalable approach empowers the rapid design and development of new treatments and increases the likelihood of success.

Our most advanced drug candidates are avapritinib, BLU-667, BLU-554 and BLU-782. Our lead drug candidate, avapritinib, is an orally available, potent and highly selective inhibitor that targets KIT and PDGFRA mutations. These mutations abnormally activate receptor tyrosine kinases that are drivers of cancer and proliferative disorders, including gastrointestinal stromal tumors, or GIST, and systemic mastocytosis, or SM. GIST is a rare disease that is a sarcoma, or tumor of bone or connective tissue, of the gastrointestinal tract, or GI tract, and SM is a rare 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 organ dysfunction and failure. We are currently evaluating avapritinib for the treatment of GIST in an ongoing Phase 1 clinical trial in advanced GIST, which we refer to

as our NAVIGATOR trial, and an ongoing global, randomized Phase 3 clinical trial comparing avapritinib to regorafenib in third-line GIST, which we refer to as our VOYAGER trial. We have completed enrollment of the NAVIGATOR trial, and we plan to present additional data from this trial in the second quarter of 2019. We expect to complete enrollment of the VOYAGER trial in the second half of 2019. We plan to initiate a Phase 3 precision medicine trial in second-line GIST in the second half of 2019, which we refer to as our COMPASS-2L trial. In addition, we plan to submit a new drug application, or NDA, for avapritinib for the treatment of PDGFRA Exon 18 mutant GIST and fourth-line GIST in the second quarter of 2019, and we plan to submit a supplemental NDA for the treatment of third-line GIST in 2020. We are currently evaluating avapritinib for the treatment of SM in an ongoing Phase 1 clinical trial in advanced SM, which we refer to as our EXPLORER trial, an ongoing registration-enabling Phase 2 clinical trial in advanced SM, which we refer to as our PATHFINDER trial, and an ongoing registration-enabling Phase 2 clinical trial in indolent and smoldering SM, which we refer to as our PIONEER trial. We plan to present updated data from the EXPLORER trial in advanced SM in the second quarter of 2019, and we plan to present initial data from the PIONEER trial in indolent and smoldering SM in the second half of 2019. We expect to complete enrollment of the PATHFINDER trial in the second half of 2019. We plan to submit an NDA for advanced SM in 2020. The U.S. Food and Drug Administration, or FDA, has granted orphan drug designation to avapritinib for the treatment of GIST and the treatment of mastocytosis, and the European Commission has granted orphan medicinal product designation to avapritinib for the treatment of GIST and the treatment of mastocytosis. The FDA has granted fast track designation to avapritinib for (i) the treatment of patients with unresectable or metastatic GIST that progressed following treatment with imatinib and a second TKI and (ii) the treatment of patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior therapy. In addition, the FDA has granted breakthrough therapy designation to avapritinib for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation and to avapritinib for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia.

BLU-667 is an orally available, potent and highly selective inhibitor that targets RET, a receptor tyrosine kinase that is abnormally activated by mutations or fusions and RET resistance mutations that we predict will arise from treatment with first generation therapies. RET drives disease in subsets of patients with non-small cell lung cancer, or NSCLC, and cancers of the thyroid, including medullary thyroid carcinoma, or MTC, and papillary thyroid cancer, or PTC, and our research suggests that RET may drive disease in subsets of patients with colon cancer, breast cancer and other cancers. We are currently evaluating BLU-667 in an ongoing Phase 1 clinical trial in patients with RET-altered NSCLC, MTC and other advanced solid tumors, which we refer to as our ARROW trial. We expect to complete enrollment of the previously treated NSCLC and MTC cohorts in the ARROW trial in the second quarter of 2019. In addition, we plan to present updated data from the ongoing ARROW trial in the second quarter of 2019. We plan to submit an NDA for BLU-667 in the first half of 2020 based on additional data from the ongoing ARROW trial and currently expect the NDA submission will be for separate potential indications: (1) patients with RET-fusion positive NSCLC who have progressed following prior systemic therapy and (2) patients with RET-mutant MTC who have progressed following treatment with a tyrosine kinase inhibitor, or TKI. In addition, in the second half of 2019, we plan to initiate a Phase 3 clinical trial evaluating BLU-667 in first-line RET-altered NSCLC and plan to initiate a Phase 2 clinical trial evaluating BLU-667 in combination with osimertinib in treatment-resistant, EGFR-mutant NSCLC harboring an acquired RET alteration. The FDA has granted orphan drug designation to BLU-667 for the treatment of RET-rearranged NSCLC, JAK1/2-positive NSCLC or TRKC-positive NSCLC, and the FDA has granted breakthrough therapy designation to BLU-667 for the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments.

BLU-554 is an 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, the most common type of liver cancer. We are currently evaluating BLU-554 in an ongoing Phase 1 clinical trial in patients with advanced HCC. We and CStone Pharmaceuticals, or CStone, plan to expand our ongoing Phase 1 clinical trial of BLU-554 to include clinical sites in Mainland China by the middle of 2019. In addition, we and CStone plan to initiate a proof-of-concept clinical trial in the second half of 2019 in the CStone territory evaluating BLU-554 in combination with CS1001, a clinical stage anti-programmed death ligand-1 immunotherapy being developed by CStone, as a first-line therapy for the treatment of patients with HCC. The FDA has granted orphan drug designation to BLU-554 for the treatment of HCC.

BLU-782 is an orally available, potent and highly selective inhibitor that targets mutant activin-like kinase 2, or ALK2. We are developing BLU-782 for the treatment of fibrodysplasia ossificans progressiva, or FOP, a rare, severely disabling genetic disease caused by mutations in the ALK2 gene, ACVR1. FOP is characterized by progressive heterotopic ossification, which is the abnormal transformation of muscle, ligaments and tendons into bone. Heterotopic

ossification may be spontaneous or associated with painful episodic disease flare-ups that are usually precipitated by soft tissue injury. As the disease progresses, extra-skeletal bone increasingly restricts joints, resulting in severe disability and loss of mobility, compromised respiratory function and increased risk of early death. Currently, there are no approved therapies for FOP. We initiated a Phase 1 clinical trial in healthy volunteers in the first quarter of 2019, and we plan to initiate a Phase 2 clinical trial evaluating BLU-782 in patients with FOP in the first half of 2020. The FDA has granted fast track designation to BLU-782 for the treatment of fibrodysplasia ossificans progressiva.

We also 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. We currently have four wholly-owned discovery programs for undisclosed kinase targets, and we anticipate nominating at least one additional wholly-owned discovery program in 2019.

In addition, we entered into collaborations with F. Hoffmann La Roche Ltd and Hoffmann La Roche Inc., which we collectively refer to as Roche, and CStone in March 2016 and June 2018, respectively. Under our collaboration agreement with Roche, we are seeking to discover, develop and commercialize up to five small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy, as single products or possibly in combination with other therapeutics. Under our collaboration agreement with CStone, we are seeking to develop and commercialize BLU-554, avapritinib and BLU-667, including back-up forms and certain other forms, in Mainland China, Hong Kong, Macau and Taiwan, or the CStone territory, either as a monotherapy or as part of a combination therapy. We will continue to evaluate additional collaborations that could maximize the value for our programs and allow us to leverage the expertise of strategic collaborators. We are also focused on engaging in collaborations to capitalize on our discovery platform outside of our primary strategic focus area of cancer.

We currently have worldwide development and commercialization rights to avapritinib, BLU-667 and BLU-554 other than the rights licensed to CStone in the CStone territory. We currently have worldwide development and commercialization rights to BLU-782 and all of our discovery programs other than the discovery-stage programs under the Roche collaboration.

To date, we have financed our operations primarily through public offerings of our common stock, private placements of our convertible preferred stock, collaborations and a debt financing. Through December 31, 2018, we have received an aggregate of \$1.1 billion from such transactions, including \$887.4 million in aggregate gross proceeds from the sale of common stock in our May 2015 initial public offering, or IPO, and December 2016, April 2017 and December 2017 follow-on public offerings, \$115.1 million in gross proceeds from the issuance of convertible preferred stock, \$18.8 million of upfront and milestone payments under our former collaboration with Alexion Pharma Holding, or Alexion, \$55.0 million in upfront and milestone payments under our existing collaboration with Roche, a \$40.0 million upfront payment under our existing collaboration with CStone, and \$10.0 million in gross proceeds from the debt financing.

Since inception, we have incurred significant operating losses. Our net losses were \$236.6 million, \$148.1 million and \$72.5 million for the years ended December 31, 2018, 2017 and 2016. As of December 31, 2018, we had an accumulated deficit of \$597.5 million. We expect to continue to incur significant expenses and operating losses over the next several years. We anticipate that our expenses will increase significantly in connection with our ongoing activities, particularly as we:

- continue to advance and initiate clinical development activities for our lead drug candidate, avapritinib, as well as our other most advanced drug candidates, BLU-667, BLU-554 and BLU-782;
- seek marketing approvals for our drug candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- continue to manufacture increasing quantities of drug substance and drug product material for use in pre-clinical studies, clinical trials and for any potential commercialization;
- continue to discover, validate and develop additional drug candidates;

- conduct research and development activities under our collaborations with Roche and CStone;
- conduct development and commercialization activities for companion diagnostic tests for current or future drug candidates;
- maintain, expand and protect our intellectual property portfolio;
- acquire or in-license other drug candidates or technologies;
- hire additional research, clinical, quality, manufacturing, regulatory, commercial and general and administrative personnel; and
- incur additional costs associated with operating as a public company.

## **Financial Operations Overview**

### ***Revenue***

To date, we have not generated any revenue from drug sales. Our revenue consists of collaboration revenue under our former collaboration with Alexion, which was terminated in October 2017, and our existing collaborations with Roche and CStone, including amounts that are recognized related to upfront payments, milestone payments and amounts due to us for research and development services. In the future, revenue may include revenues related to the supply of our drug candidates or products to CStone for development and commercialization activities in the CStone territory and additional milestone payments and royalties on any net product sales under our collaborations with Roche and CStone. We do not expect to generate any revenue from the sale of avapritinib until 2020, assuming we are able to file for regulatory approval for avapritinib in the United States in the second quarter of 2019 and receive marketing approval by 2020. We expect that any revenue we generate will fluctuate from quarter to quarter as a result of the timing and amount of product sales, if any, license fees, research and development services and related reimbursements, payments for manufacturing services, and milestone and other payments.

In the future, subject to obtaining marketing approval for one or more of our drug candidates, we expect to generate revenue from a combination of product sales, royalties on product sales and cost reimbursements, as well as upfront, milestone and royalty payments, if any, under any current or future collaborations

### ***Expenses***

#### *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:

- employee-related expenses including salaries, benefits, and stock-based compensation expense;
- expenses incurred under agreements with third parties that conduct research and development, pre-clinical activities, clinical activities and manufacturing on our behalf;
- expenses incurred under agreements with third parties for the development and commercialization of companion diagnostic tests;
- the cost of consultants;
- the cost associated with regulatory quality assurance and quality control operations;
- the cost of lab supplies and acquiring, developing and manufacturing pre-clinical 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 our drug candidates. 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 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 our drug candidates;
- commercializing the drug candidates, if and when approved, whether alone or in collaboration with others; 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. 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 drug candidates, 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, 2018, 2017 and 2016. Other development and pre-development candidate expenses, unallocated expenses and internal research and development expenses have been classified separately.

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Avapritinib external expenses	\$ 83,417	\$ 46,851	10,653
BLU-554 external expenses	10,167	15,078	13,160
BLU-667 external expenses	44,099	13,512	6,599
BLU-782 external expenses	9,720	1,114	—
Other development and pre-development candidate expenses and unallocated expenses	46,988	39,981	32,232
Internal research and development expenses	49,230	28,151	18,487
<b>Total research and development expenses</b>	<b>\$ 243,621</b>	<b>\$ 144,687</b>	<b>\$ 81,131</b>

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 drug product and drug substance manufacturing expenses for current and future clinical trials. 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 collaboration with Roche, development activities under our collaboration with CStone and development activities for companion diagnostic tests for current and future drug candidates.

#### *General and Administrative Expenses*

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, 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, pre-commercial development activities, legal fees relating to intellectual property and corporate matters and fees for accounting and consulting services.

We expect that our general and administrative expenses will increase in the future to support continued research and development activities and planned commercialization activities, including establishing a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval. 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.

#### *Other Income (Expense), net*

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

#### *Interest Expense*

Interest expense consists primarily of interest expense on amounts outstanding under a loan and security agreement that we entered into with Silicon Valley Bank in May 2013 and amortization of debt discount. We made our final loan payment in 2018, and as of December 31, 2018, we had no outstanding principal and interest under the loan and security agreement.

#### *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. Actual results may differ from these estimates under different assumptions or conditions. On an ongoing basis, we evaluate our judgments and estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates, if any, will be reflected in the consolidated financial statements prospectively from the date of change in estimates.

Our critical accounting policies are those policies that require the most significant judgments and estimates in the preparation of our financial statements. Management has determined that our most critical accounting policies are those relating to revenue recognition, accrued research and development expenses, available-for-sale investments and stock-based compensation.

#### *Revenue Recognition*

Effective January 1, 2018, we adopted Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers*, which we refer to as ASC 606, using the modified retrospective transition method. Under this method, results for reporting periods beginning after January 1, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with ASC Topic 605, *Revenue Recognition*. We only applied the modified retrospective transition method to contracts that were not completed as January 1, 2018, the effective date of adoption for ASC 606. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity 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 entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

We enter into licensing agreements that are within the scope of ASC 606, under which we may exclusively license rights to research, develop, manufacture and commercialize our product candidates to third parties. The terms of these arrangements typically include payment of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under our agreements, we perform 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) we satisfy each performance obligation. As part of the accounting for these arrangements, we must use significant judgment to determine: (a) the number of 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. We use 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 we recognize revenue as or when the performance obligations under the contract are satisfied.

Amounts received prior to revenue recognition are recorded as deferred revenue. 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.

*Exclusive Licenses.* If the license to our intellectual property is determined to be distinct from the other promises or performance obligations identified in the arrangement, we recognize 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, we consider 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, we consider 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, we utilize 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. We evaluate 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 we record in future periods.

*Research and Development Services.* The promises under our collaboration agreements may include research and development services to be performed by our employees on behalf of the partner. Payments or reimbursements resulting from our research and development efforts are recognized as the services are performed and presented on a gross basis because we are the principal for such efforts. Reimbursements from and payments to 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. We evaluate 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. We allocate 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, we evaluate 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 our control or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. We evaluate 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, we reevaluate 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, we recognize 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, we have not recognized any royalty revenue resulting from any of our licensing arrangements.

*Collaborative Arrangements.* We analyze our 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 808, *Collaborative Arrangements*, which we refer to as 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, we first determine 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, generally by analogy to ASC 606. Amounts that are owed to collaboration partners are recognized as an offset to collaboration revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed our collaboration revenues in each quarterly period, such amounts are classified as research and development expense. For those elements of the arrangement that are accounted for pursuant to ASC 606, we apply the five-step model described above under ASC 606.

#### *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.

#### *Available-for-Sale Investments*

We classify marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current. Available-for-sale securities are maintained by an investment manager and may consist of U.S. Treasury securities and U.S. government agency securities. Available-for-sale 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). If any adjustment to fair value reflects a decline in value of the investment, we consider all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, mark the investment to market through a charge to our consolidated statement of operations and comprehensive loss.

#### *Stock-Based Compensation*

We account for stock-based compensation awards in accordance with ASC 718, *Compensation – Stock Compensation*, or ASC 718. We expense 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. Prior to 2017, expense was recognized net of estimated forfeitures and adjusted to reflect actual forfeitures. Effective January 1, 2017, upon adoption of ASU No. 2016-09, *Compensation – Stock Compensation* under the modified retrospective approach, we began recognizing gross stock compensation expense with actual forfeitures recognized as they occur. Compensation cost for restricted stock awards issued to employees is measured using the grant date intrinsic value of the award and is adjusted to reflect actual forfeitures. We estimate the fair value of options granted to employees at the date of grant using the Black-Scholes option-pricing model that requires management to apply judgment and make estimates, including:

- expected volatility, which is calculated based on reported volatility data for a representative group of publicly traded companies for which historical information is available. For these analyses, we select companies with comparable characteristics to ours 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. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. We intend to consistently apply this process using representative companies until a sufficient amount of historical information regarding the volatility of our own share price becomes available;
- 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 we calculate using the simplified method, as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share-Based Payment*, as we have insufficient historical information regarding our 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;
- dividend yield, which is zero based on the fact that we never paid cash dividends and do 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 of the intrinsic value of equity instruments issued, whichever is more reliably measured. The measurement date for non-employee awards is the date of grant without changes in the fair value of the award. 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 our 2015 employee stock purchase plan, or 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 our 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.

**Results of Operations****Comparison of Years Ended December 31, 2018 and 2017**

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Dollar Change	% Change
	2018	2017 (in thousands)		
Collaboration revenue	\$ 44,521	\$ 21,426	\$ 23,095	108 %
Operating expenses:				
Research and development	243,621	144,687	98,934	68
General and administrative	47,928	27,986	19,942	71
Total operating expenses	291,549	172,673	118,876	69
Other income (expense):				
Other income (expense), net	10,459	3,349	7,110	212
Interest expense	(73)	(221)	148	(67)
Total other income (expense)	10,386	3,128	7,258	232
Net loss	<u>\$ (236,642)</u>	<u>\$ (148,119)</u>	<u>\$ (88,523)</u>	<u>60 %</u>

*Collaboration Revenue*

Collaboration revenue increased by \$23.1 million from \$21.4 million for the year ended December 31, 2017 to \$44.5 million for the year ended December 31, 2018. Collaboration revenue for the year ended December 31, 2018 was related to the CStone and Roche agreements. Collaboration revenue for the year ended December 31, 2017 was related to the Roche and Alexion agreements. We recorded \$4.5 million and \$5.2 million in collaboration revenue under the Roche agreement for the years ended December 31, 2018 and December 31, 2017, respectively. The decrease was primarily due to the adoption of ASC 606 on January 1, 2018 and the resulting change in the revenue recognition pattern. We entered into the CStone agreement on June 1, 2018 and recorded collaboration revenue of \$40.0 million under the CStone agreement for the year ended December 31, 2018. We recorded collaboration revenue of \$16.2 million under the Alexion agreement for the year ended December 31, 2017. As a result of the termination of the agreement during 2017, we did not recognize any revenue under the Alexion agreement for the year ended December 31, 2018.

*Research and Development Expense*

Research and development expense increased by \$98.9 million from \$144.7 million for the year ended December 31, 2017 to \$243.6 million for the year ended December 31, 2018. The increase in research and development expense was primarily related to the following:

- approximately \$35.3 million in increased expenses for external clinical activities related to avapritinib and BLU-667;
- approximately \$27.5 million in increased personnel expense, primarily due to an increase in headcount, which was driven by growth in the clinical and manufacturing organizations as we advance our lead drug candidates, and an increase of \$10.7 million in stock-based compensation expense;
- approximately \$27.3 million in increased expenses associated with clinical and commercial manufacturing activities;
- approximately \$5.6 million in increased expenses associated with continuing to build our discovery platform and advance our discovery pipeline; and
- approximately \$2.8 million in increased toxicology studies, including IND-enabling pre-clinical studies related to BLU-782.

*General and Administrative Expense*

General and administrative expense increased by \$19.9 million from \$28.0 million for the year ended December 31, 2017 to \$47.9 million for the year ended December 31, 2018. The increase in general and administrative expense was primarily related to the following:

- approximately \$11.1 million in increased personnel expenses, primarily due to an increase in general and administrative headcount to support our overall growth as a publicly traded company and an increase of \$7.3 million in stock-based compensation expense;
- approximately \$6.1 million in increased professional fees including pre-commercial planning activities; and
- approximately \$2.1 million in increased facility costs related to our new headquarters in 2018.

*Other Income (Expense), Net*

Other income, net, increased by \$7.1 million from \$3.3 million for the year ended December 31, 2017 to \$10.5 million for the year ended December 31, 2018. The increase was primarily related to higher average investment balances and a higher rate of return on investments.

*Interest Expense*

Interest expense decreased by \$0.1 million from \$0.2 million for the year ended December 31, 2017 to \$0.1 million for the year ended December 31, 2018. The decrease was primarily related to a decrease in the average outstanding principle balance under the loan and security agreement with Silicon Valley Bank for the year ended December 31, 2018. We made our final loan payment in 2018, and as of December 31, 2018, we had no outstanding principal and interest under the loan and security agreement.

**Comparison of Years Ended December 31, 2017 and 2016**

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016, together with the changes in those items in dollars and as a percentage:

	<b>Year Ended December 31,</b>		<b>Dollar Change</b>	<b>% Change</b>
	<u>2017</u>	<u>2016</u>		
	<b>(in thousands)</b>			
Collaboration revenue	\$ 21,426	\$ 27,772	\$ (6,346)	(23)%
Operating expenses:				
Research and development	144,687	81,131	63,556	78
General and administrative	27,986	19,218	8,768	46
Total operating expenses	172,673	100,349	72,324	72
Other income (expense):				
Other income (expense), net	3,349	551	2,798	508
Interest expense	(221)	(469)	248	(53)
Total other income (expense)	3,128	82	3,046	3,715
Net loss	<u>\$ (148,119)</u>	<u>\$ (72,495)</u>	<u>\$ (75,624)</u>	<u>104 %</u>

*Collaboration Revenue*

Collaboration revenue decreased by \$6.3 million from \$27.8 million for the year ended December 31, 2016 to \$21.4 million for the year ended December 31, 2017. Collaboration revenue for the year ended December 31, 2017 was related to the former collaboration with Alexion and the existing collaboration with Roche. We recorded collaboration revenue of \$16.2 million and \$23.3 million under the Alexion collaboration for the years ended December 31, 2017 and December 31, 2016, respectively. Collaboration revenue under our former collaboration with Alexion began in March

2015 upon the execution of the Alexion collaboration agreement. The decrease was primarily due to lower reimbursable research and development expenses as a result of the termination of the agreement and the impact of the recognition of two milestone payments upon achievement included in the year ended December 31, 2016. As a result of the termination of the Alexion collaboration, we recognized the remaining deferred revenue balance related to the upfront payment and non-substantive milestone payment previously received under the collaboration utilizing the proportional performance model over the remaining period of performance, which ended October 24, 2017. We entered into the Roche agreement in March 2016 and recorded \$5.2 million and \$4.5 million in collaboration revenue under the Roche collaboration for the year ended December 31, 2017 and December 31, 2016, respectively.

#### *Research and Development Expense*

Research and development expense increased by \$63.6 million from \$81.1 million for the year ended December 31, 2016 to \$144.7 million for the year ended December 31, 2017. The increase in research and development expense was primarily related to the following:

- approximately \$24.7 million in increased expenses associated with clinical and commercial manufacturing activities;
- approximately \$20.3 million in increased expenses for external clinical activities related to avapritinib, BLU-667 and BLU-554, further through Phase 1 clinical trials;
- approximately \$15.0 million in increased personnel expense primarily due to a 35% increase in headcount and an increase of \$3.6 million in stock-based compensation expense, which were driven by growth in the clinical and manufacturing organizations; and
- approximately \$0.9 million in increased expenses associated with continuing to build our discovery platform and advance our discovery pipeline.

#### *General and Administrative Expense*

General and administrative expense increased by \$8.8 million from \$19.2 million for the year ended December 31, 2016 to \$28.0 million for the year ended December 31, 2017. The increase in general and administrative expense was primarily related to the following:

- approximately \$5.1 million in increased personnel expenses due to an increase of 35% in general and administrative headcount to support our overall growth as a publicly traded company and an increase of \$2.8 million in stock-based compensation expense; and
- approximately \$2.8 million in increased professional fees including market research and public relations costs.

#### *Other Income (Expense), Net*

Other income (expense), net, increased by \$2.8 million from \$0.6 million of expense for the year ended December 31, 2016 to \$3.3 million of income for the year ended December 31, 2017. The increase in other income, net, was primarily related to an increase in investment income during the year ended December 31, 2017.

#### *Interest Expense*

Interest expense decreased by \$0.2 million from \$0.5 million for the year ended December 31, 2016 to \$0.2 million for the year ended December 31, 2017. The decrease was primarily related to a decrease in the average outstanding principle balance under the loan and security agreement with Silicon Valley Bank for the year ended December 31, 2017. We made our final loan payment in 2018, and as of December 31, 2018, we had no outstanding principal and interest under the loan and security agreement.

## 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 stock, collaborations and a debt financing.

Through December 31, 2018, we have received an aggregate of \$1.1 billion from such transactions, including \$887.4 million in aggregate gross proceeds from the sale of common stock in our May 2015 IPO and December 2016, April 2017 and December 2017 follow-on public offerings, \$115.1 million in gross proceeds from the issuance of convertible preferred stock, \$18.8 million of upfront and milestone payments from Alexion, \$55.0 million in upfront and milestone payments from Roche, a \$40.0 million upfront payment under our existing collaboration with CStone and \$10.0 million in gross proceeds from the debt financing.

As of December 31, 2018, we had cash, cash equivalents and investments of \$494.0 million.

### Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2018, 2017 and 2016

(in thousands)	Year Ended December 31,		
	2018	2017	2016
Net cash used in operating activities	\$ (175,009)	\$ (119,865)	\$ (24,513)
Net cash used in investing activities	(161,088)	(72,347)	(218,821)
Net cash provided by financing activities	4,454	543,948	132,577
Net increase (decrease) in cash and cash equivalents	\$ (331,643)	\$ 351,736	\$ (110,757)

*Net Cash Used in Operating Activities.* For the year ended December 31, 2018, compared to the same period in 2017, the \$55.1 million increase in net cash used in operating was primarily due to the increase in net loss during this period of \$88.5 million, which was driven by increased payroll and payroll-related expenses and spending on pre-clinical, clinical and pre-commercial activities, partially offset by upfront and milestone payments received during year ended December 31, 2018. The net cash flows provided by operating activities for year ended December 31, 2018 reflect a \$40.0 million upfront payment received under the CStone agreement and a \$10.0 million milestone payment received under the Roche agreement. We did not receive any upfront payments or milestones during year ended December 31, 2017.

For the year ended December 31, 2017, compared to the same period in 2016, the \$95.4 million increase in net cash used in operating activities was primarily due to an increase in net loss of \$75.6 million for the year end December 31, 2017 as compared to the year ended December 31, 2016 as well as changes in deferred revenue related to the timing and amount of upfront payment from Roche. In the year ended December 31, 2016, we received a \$45.0 million upfront payment from Roche compared to no upfront payments received during the year ended December 31, 2017.

*Net Cash Used in Investing Activities.* For the year ended December 31, 2018, compared to the same period in 2017, the \$88.7 million increase in net cash used in investing activities was primarily due to an increase in net purchases of available-for-sale investments.

For the year ended December 31, 2017, compared to the same period in 2016, the \$146.5 million decrease in net cash used in investing activities was primarily due to a decrease in net purchases of available-for-sale investments which was partially offset by purchases of property and equipment that mainly related to the relocation of our headquarters.

*Net Cash Provided by Financing Activities.* For the year ended December 31, 2018, compared to the same period in 2017, the \$539.5 million decrease in net cash provided by financing activities was primarily due to a total of \$541.5 million decrease in net proceeds received from our April 2017 and December 2017 follow-on underwritten public offerings, after deducting underwriting discounts and commissions and offering expenses paid by us, partially offset by proceeds received from stock option exercises.

For the year ended December 31, 2017, compared to the same period in 2016, the \$411.4 million increase in net cash provided by financing activities was primarily due to \$406.3 million increase in net proceeds from public offerings, after deducting underwriting discounts and commissions and offering expenses payable by us, and \$4.3 million increase in proceeds received for the issuance of common stock.

#### *Borrowings*

In May 2013, we entered into the loan and security agreement with Silicon Valley Bank. Under the terms of the loan and security agreement, we borrowed \$5.0 million. Loan advances under the loan and security agreement accrue interest at a fixed rate of 2.0% above the prime rate. In November 2014, we amended the loan and security agreement and borrowed an additional \$5.0 million. Each loan advance included an interest-only payment period. During the years ended December 31, 2018, 2017, and 2016, we paid principal payments of \$1.5 million, \$2.6 million, and \$3.3 million, respectively, on the \$10.0 million of advances. We were required to pay a fee of 4% of the total loan advances at the end of the term of the loan. There were no financial covenants associated with the loan and security agreement. As of December 31, 2018, we had no outstanding principal and interest under the loan and security agreement.

See Note 9, "Term Loan," in the accompanying notes to our audited consolidated financial statements for additional information.

#### *Funding Requirements*

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, continue and initiate clinical trials of, and seek marketing approval for, our drug candidates. In addition, if we obtain marketing approval for any of our drug candidates, we expect to incur significant commercialization expenses related to drug sales, marketing, manufacturing and distribution to the extent that such sales, marketing and distribution are not the responsibility of potential collaborators. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

As of December 31, 2018, we had cash, cash equivalents and investments of \$494.0 million. Based on our current plans, we believe that our existing cash, cash equivalents and investments, excluding any potential option fees and milestone payments under our existing collaborations with Roche and CStone, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the second half of 2020. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, pre-clinical development, laboratory testing and clinical trials for our drug candidates;
- the costs of securing and producing drug substance and drug product material for use in pre-clinical studies, clinical trials and for use as commercial supply;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our drug candidates;
- the success of our collaborations with Roche and CStone;
- the success of our current or future companion diagnostic test collaborations for companion diagnostic tests;
- our ability to establish and maintain collaborations on favorable terms, if at all;

- the achievement of milestones or occurrence of other developments that trigger payments under our collaboration agreements with Roche and CStone or any collaboration agreements that we may enter into in the future;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other drug candidates and technologies;
- the costs of securing manufacturing arrangements for development activities and commercial production;
- the costs of establishing operations outside the United States; and
- the costs of establishing or contracting for sales, marketing and distribution capabilities if we obtain regulatory approvals to market our drug candidates.

Identifying potential drug candidates and conducting pre-clinical development and testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve drug sales. In addition, our drug candidates, if approved, may not achieve commercial success. Accordingly, we will need to continue 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 through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. At this time, we do not have any committed external source of funds other than potential funds to be earned under our collaborations with Roche and CStone. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, 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 technologies, future revenue streams, research programs 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 candidates that we would otherwise prefer to develop and market ourselves.

### Contractual Obligations

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2018:

(in thousands)	Payments Due by Period				
	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
Operating lease obligations (1)	\$ 154,358	\$ 9,822	\$ 27,628	\$ 28,635	\$ 88,273
Capital lease obligations	136	136	-	-	-
<b>Total</b>	<b>\$ 154,494</b>	<b>\$ 9,958</b>	<b>\$ 27,628</b>	<b>\$ 28,635</b>	<b>\$ 88,273</b>

(1) Represents future minimum lease payments under our non-cancelable operating leases, net of payments under our sublease for the office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

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 pre-clinical research studies, synthetic chemistry and other services and products for operating purposes. We have not included these payments in the table of 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 lead drug candidates. We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not fixed and determinable.

#### **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, 2018 and December 31, 2017, we had cash, cash equivalents and investments of \$494.0 million and \$673.4 million, respectively, consisting primarily of money market funds and investments in U.S. 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, particularly because our investments are in short-term marketable securities. 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. From time to time, we contract with vendors that are located 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, 2018 and December 31, 2017, we had minimal or no liabilities denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor and clinical trial 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, 2018 and 2017.

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

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15 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, 2018. Based upon such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2018, 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, 2018 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, 2018.

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**

The Board of Directors and Stockholders 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, 2018, 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, 2018, 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, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, and the related notes and our report dated February 26, 2019 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 26, 2019

### **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, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

### **Item 9B. Other Information**

On February 25, 2019, we entered into a fourth amendment to our collaboration and license agreement, as amended, with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., which we refer to collectively as Roche, pursuant to which we and Roche agreed to modify certain time periods related to Roche's option rights for one of the collaboration programs and to modify certain time periods related to the screening activities under the collaboration.

The foregoing description of the fourth amendment to the collaboration and license agreement with Roche is qualified in its entirety by reference to the complete text of such agreement, a copy of which is attached as Exhibit 10.26 to this Annual Report on Form 10-K.

## **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 2019 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 2019 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 2019 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 2019 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 2019 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-33 attached hereto and are filed as part of this Annual Report on Form 10-K.

<a href="#">Report of Independent Registered Public Accounting Firm</a>	F-2
<a href="#">Consolidated Balance Sheets</a>	F-3
<a href="#">Consolidated Statements of Operations and Comprehensive Loss</a>	F-4
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## (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	
3.1	<a href="#">Fifth Amended and Restated Certificate of Incorporation of the Registrant</a>	10-Q	001-37359	3.1	November 9, 2015
3.2	<a href="#">Amended and Restated Bylaws of the Registrant</a>	10-Q	001-37359	3.2	November 9, 2015
4.1	<a href="#">Specimen Common Stock Certificate</a>	S-1/A	333-202938	4.1	April 20, 2015
4.2	<a href="#">Second Amended and Restated Investors' Rights Agreement, dated as of November 7, 2014, by and among the Registrant and the Investors listed therein</a>	S-1	333-202938	4.4	March 23, 2015
10.1#	<a href="#">2011 Stock Option and Grant Plan, as amended, and forms of award agreements thereunder</a>	S-1	333-202938	10.1	March 23, 2015
10.2#	<a href="#">2015 Stock Option and Incentive Plan and forms of award agreements thereunder</a>	10-K	001-37359	10.2	March 11, 2016
10.3#	<a href="#">Form of non-qualified stock option agreement for employees under 2015 Stock Option and Incentive Plan</a>	10-Q	001-37359	10.2	August 1, 2018
10.4#	<a href="#">Form of non-qualified stock option agreement for consultants under 2015 Stock Option and Incentive Plan</a>	10-Q	001-37359	10.3	August 1, 2018
10.5#	<a href="#">Form of restricted stock unit award agreement for employees under 2015 Stock Option and Incentive Plan</a>	10-Q	001-37359	10.4	August 1, 2018
10.6#	<a href="#">Form of restricted stock unit award agreement for non-employee directors under 2015 Stock Option and Incentive Plan</a>	10-Q	001-37359	10.5	August 1, 2018

Exhibit Number	Description of Exhibit	Incorporated by Reference			Filing Date
		Form	File No.	Exhibit Number	
10.7#	<a href="#">Form of restricted stock unit award agreement for consultants under 2015 Stock Option and Incentive Plan</a>	10-Q	001-37359	10.6	August 1, 2018
10.8#	<a href="#">2015 Employee Stock Purchase Plan</a>	S-8	333-203749	99.3	April 30, 2015
10.9	<a href="#">Lease Agreement, dated February 11, 2015, by and between the Registrant and 38 Sidney Street Limited Partnership</a>	S-1	333-202938	10.4	March 23, 2015
10.10	<a href="#">First Amendment to Lease Agreement, dated January 26, 2018, by and between the Registrant and 38 Sidney Street Limited Partnership</a>	10-K	001-37359	10.5	February 26, 2019
10.11	<a href="#">Lease Agreement, dated April 28, 2017, by and between the Registrant and UP 45/75 Sidney Street, LLC</a>	10-Q	001-37359	10.1	May 3, 2017
10.12	<a href="#">First Amendment of Lease, dated September 19, 2018, between Blueprint Medicines Corporation and UP 45/75 Sidney Street, LLC</a>	8-K	001-37359	10.1	September 25, 2018
10.13#	<a href="#">Employment Agreement, dated November 6, 2015, by and between the Registrant and Jeffrey W. Albers</a>	10-Q	001-37359	10.2	November 9, 2015
10.14#	<a href="#">Employment Agreement, dated November 6, 2015, by and between the Registrant and Anthony L. Boral</a>	10-Q	001-37359	10.4	November 9, 2015
10.15#	<a href="#">Employment Agreement, dated March 10, 2016, by and between the Registrant and Kathryn Haviland</a>	10-K	001-37359	10.9	March 11, 2016
10.16#	<a href="#">First Amendment to Employment Agreement, dated January 30, 2019, by and between the Registrant and Kathryn Haviland</a>	8-K	001-37359	10.2	February 5, 2019
10.17#	<a href="#">Employment Agreement, dated September 6, 2016, by and between the Registrant and Tracey L. McCain</a>	10-Q	001-37359	10.3	November 10, 2016
10.18#	<a href="#">Employment Agreement, dated November 9, 2016, by and between the Registrant and Marion Dorsch</a>	8-K	001-37359	10.1	November 14, 2016
10.19#	<a href="#">Employment Agreement, dated October 10, 2017, by and between the Registrant and Christopher Murray</a>	10-Q	001-37359	10.1	October 31, 2017
10.20#	<a href="#">Employment Agreement, dated November 22, 2017, by and between the Registrant and Michael Landsittel</a>	8-K	001-37359	10.1	November 22, 2017
10.21#	<a href="#">First Amendment to Employment Agreement, dated January 30, 2019, by and between the Registrant and Michael Landsittel</a>	8-K	001-37359	10.1	February 5, 2019
10.22#	<a href="#">Employment Agreement, dated October 29, 2018, by and between the Registrant and Christina Rossi</a>	8-K	001-37359	10.1	October 29, 2018
10.23†	<a href="#">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</a>	10-Q/A	001-37359	10.2	July 22, 2016

Exhibit Number	Description of Exhibit	Incorporated by Reference			Filing Date
		Form	File No.	Exhibit Number	
10.24†	<a href="#">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</a>	10-Q	001-37359	10.1	August 9, 2016
10.25	<a href="#">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</a>	10-Q	001-37359	10.1	November 10, 2016
10.26	<a href="#">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</a>				*
10.27†	<a href="#">License and Collaboration Agreement, dated June 1, 2018, between the Registrant and CStone Pharmaceuticals</a>	10-Q	001-37359	10.1	August 1, 2018
10.28	<a href="#">Form of Indemnification Agreement entered into between the Registrant and its directors</a>	S-1	333-202938	10.11	March 23, 2015
10.29	<a href="#">Form of Indemnification Agreement entered into between the Registrant and its officers</a>	S-1	333-202938	10.12	March 23, 2015
10.30	<a href="#">Senior Executive Cash Incentive Bonus Plan</a>	10-K	001-37359	10.15	March 11, 2016
21.1	<a href="#">Subsidiaries of the Registrant</a>				*
23.1	<a href="#">Consent of Ernst &amp; Young LLP</a>				*
31.1	<a href="#">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</a>				*
31.2	<a href="#">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</a>				*
32.1	<a href="#">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</a>				+
101.INS	XBRL Instance 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				*

# Indicates management contract or compensatory plan or arrangement.

† Confidential treatment requested as to portions of the exhibit. Confidential materials omitted and filed separately with the Securities and Exchange Commission.

\* 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 26, 2019

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.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Jeffrey W. Albers</u> Jeffrey W. Albers	President, Chief Executive Officer and Director (Principal Executive Officer)	February 26, 2019
<u>/s/ Michael Landsittel</u> Michael Landsittel	Chief Financial Officer (Principal Financial and Accounting Officer)	February 26, 2019
<u>/s/ Daniel S. Lynch</u> Daniel S. Lynch	Chairman of the Board	February 26, 2019
<u>/s/ Nicholas Lydon</u> Nicholas Lydon, Ph.D.	Director	February 26, 2019
<u>/s/ Alexis Borisy</u> Alexis Borisy	Director	February 26, 2019
<u>/s/ Mark Goldberg</u> Mark Goldberg, M.D.	Director	February 26, 2019
<u>/s/ Charles A. Rowland, Jr.</u> Charles A. Rowland, Jr.	Director	February 26, 2019
<u>/s/ George Demetri</u> George Demetri, M.D.	Director	February 26, 2019
<u>/s/ Lonnel Coats</u> Lonnel Coats	Director	February 26, 2019
<u>/s/ Lynn Seely</u> Lynn Seely, M.D.	Director	February 26, 2019

**Blueprint Medicines Corporation**

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## Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders 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, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, 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, 2018, 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 26, 2019 expressed an unqualified opinion thereon.

### ***Adoption of ASC 606***

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, Revenue from Contracts with Customers (Topic 606), and the related amendments.

### ***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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2011.

Boston, Massachusetts  
February 26, 2019

**Blueprint Medicines Corporation**  
**Consolidated Balance Sheets**  
**(in thousands, except share and per share data)**

	<b>December 31, 2018</b>	<b>December 31, 2017</b>
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 68,064	\$ 400,304
Investments, available-for-sale	425,948	273,052
Prepaid expenses and other current assets	5,775	12,149
Total current assets	499,787	685,505
Property and equipment, net	29,627	24,363
Restricted cash	5,154	4,555
Other assets	5,556	1,314
Total assets	<u>\$ 540,124</u>	<u>\$ 715,737</u>
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable	3,298	3,744
Accrued expenses	51,711	30,541
Current portion of deferred revenue	3,600	5,373
Current portion of lease incentive obligation	1,714	1,714
Current portion of term loan payable	—	1,518
Total current liabilities	60,323	42,890
Deferred rent, net of current portion	5,130	4,129
Deferred revenue, net of current portion	42,567	30,000
Lease incentive obligation, net of current portion	12,903	14,617
Other long-term liabilities	192	131
Total liabilities	121,115	91,767
Commitments (Note 14)		
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; 44,037,026 and 43,577,526 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	44	43
Additional paid-in capital	1,016,690	979,785
Accumulated other comprehensive loss	(180)	(269)
Accumulated deficit	(597,545)	(355,589)
Total stockholders' equity	419,009	623,970
Total liabilities and stockholders' equity	<u>\$ 540,124</u>	<u>\$ 715,737</u>

**Blueprint Medicines Corporation**  
**Consolidated Statements of Operations and Comprehensive Loss**  
**(in thousands, except per share data)**

	2018	Year Ended December 31, 2017	2016
Collaboration revenue	\$ 44,521	\$ 21,426	\$ 27,772
Operating expenses:			
Research and development	243,621	144,687	81,131
General and administrative	47,928	27,986	19,218
Total operating expenses	291,549	172,673	100,349
Other income (expense):			
Other income (expense), net	10,459	3,349	551
Interest expense	(73)	(221)	(469)
Total other income (expense)	10,386	3,128	82
Net loss	\$ (236,642)	\$ (148,119)	\$ (72,495)
Other comprehensive loss:			
Changes in foreign currency translation adjustments	(16)	—	—
Changes in unrealized losses related to available-for-sale investments	105	(251)	(18)
Comprehensive loss	\$ (236,553)	\$ (148,370)	\$ (72,513)
Net loss per share — basic and diluted	\$ (5.39)	\$ (3.92)	\$ (2.64)
Weighted-average number of common shares used in net loss per share — basic and diluted	43,867	37,793	27,492

**Blueprint Medicines Corporation**  
**Consolidated Statements of Stockholders' Equity**  
(in thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2015	27,065,558	\$ 27	\$ 278,927	\$ —	\$ (134,975)	\$ 143,979
Follow on offering, net of issuance costs	5,750,000	6	134,543	—	—	134,549
Issuance of common stock under stock plan	284,471	—	546	—	—	546
Purchase of common stock under ESPP	23,325	—	377	—	—	377
Stock-based compensation expense	—	—	6,140	—	—	6,140
Unrealized loss on available-for-sale securities	—	—	—	(18)	—	(18)
Net loss	—	—	—	—	(72,495)	(72,495)
Balance at December 31, 2016	33,123,354	\$ 33	\$ 420,533	\$ (18)	\$ (207,470)	\$ 213,078
Follow on offering, net of issuance costs	10,009,259	10	541,366	—	—	541,376
Issuance of common stock under stock plan	428,210	—	4,887	—	—	4,887
Purchase of common stock under ESPP	16,703	—	476	—	—	476
Stock-based compensation expense	—	—	12,523	—	—	12,523
Unrealized loss on available-for-sale securities	—	—	—	(251)	—	(251)
Net loss	—	—	—	—	(148,119)	(148,119)
Balance at December 31, 2017	43,577,526	43	979,785	(269)	(355,589)	623,970
Issuance of common stock under stock plan	445,622	1	5,586	—	—	5,587
Purchase of common stock under ESPP	13,878	—	750	—	—	750
Stock-based compensation expense	—	—	30,534	—	—	30,534
Adoption of new accounting standard	—	—	—	—	(5,314)	(5,314)
Cumulative translation adjustment	—	—	—	(16)	—	(16)
Unrealized loss on available-for-sale securities	—	—	—	105	—	105
Other	—	—	35	—	—	35
Net loss	—	—	—	—	(236,642)	(236,642)
Balance at December 31, 2018	<u>44,037,026</u>	<u>\$ 44</u>	<u>\$ 1,016,690</u>	<u>\$ (180)</u>	<u>\$ (597,545)</u>	<u>\$ 419,009</u>

**Blueprint Medicines Corporation**  
**Consolidated Statements of Cash Flows**  
(in thousands)

	Year Ended December 31,		
	2018	2017 (as adjusted)	2016 (as adjusted)
<b>Cash flows from operating activities</b>			
Net loss	\$ (236,642)	\$ (148,119)	\$ (72,495)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	4,246	1,578	1,582
Stock-based compensation	30,534	12,523	6,140
Accretion of premiums and discounts on investments	(4,381)	(320)	301
Other	(6)	32	73
<b>Changes in assets and liabilities:</b>			
Prepaid expenses and other current assets	6,284	(3,689)	1,307
Other assets	(4,242)	(458)	(304)
Accounts payable	(445)	1,532	4
Accrued expenses	24,804	14,597	5,773
Deferred revenue	5,479	(11,861)	33,594
Deferred rent	(640)	14,320	(488)
Net cash used in operating activities	<u>(175,009)</u>	<u>(119,865)</u>	<u>(24,513)</u>
<b>Cash flows from investing activities</b>			
Purchases of property and equipment	(12,677)	(15,512)	(2,354)
Purchases of investments	(801,236)	(360,835)	(264,467)
Maturities of investments	652,825	304,000	48,000
Net cash used in investing activities	<u>(161,088)</u>	<u>(72,347)</u>	<u>(218,821)</u>
<b>Cash flows from financing activities</b>			
Principal payments on loan payable	(1,528)	(2,583)	(3,333)
Principal payments on capital lease obligations	(162)	—	—
Payment of offering costs	(281)	(965)	(143)
Proceeds from public offerings of common stock, net of commissions and underwriting discounts	—	542,225	135,125
Proceeds from issuance of common stock	6,425	5,271	928
Net cash provided by financing activities	<u>4,454</u>	<u>543,948</u>	<u>132,577</u>
Net increase (decrease) in cash, cash equivalents, and restricted cash	(331,643)	351,736	(110,757)
Cash, cash equivalents and restricted cash at beginning of period	405,072	53,336	164,093
Cash, cash equivalents and restricted cash at end of period	<u>\$ 73,429</u>	<u>\$ 405,072</u>	<u>\$ 53,336</u>
<b>Supplemental cash flow information</b>			
Public offering costs incurred but unpaid at period end	<u>\$ —</u>	<u>\$ 317</u>	<u>\$ 433</u>
Property and equipment purchases unpaid at period end	<u>\$ 912</u>	<u>\$ 3,947</u>	<u>\$ —</u>
Cash paid for interest	<u>\$ 267</u>	<u>\$ 151</u>	<u>\$ 316</u>

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, 2018	December 31, 2017	December 31, 2016
Cash and cash equivalents	68,064	400,304	52,069
Restricted cash included in prepaid expenses and other current assets	211	213	—
Restricted cash	5,154	4,555	1,267
Total cash, cash equivalents, and restricted cash shown in consolidated statements of cash flows	<u>73,429</u>	<u>405,072</u>	<u>53,336</u>

**Blueprint Medicines Corporation**  
**Notes to Consolidated Financial Statements**

**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, rare diseases and cancer immunotherapy. The Company's approach is to leverage its novel target discovery engine to systematically and reproducibly identify kinases that are drivers of diseases and to craft highly selective and potent drug candidates that may provide significant and durable clinical responses for patients without adequate treatment options.

The Company is devoting substantially all of its efforts to research and development, initial market development and raising capital. The Company is subject to a number of risks similar to those of other early stage companies, including dependence on key individuals; establishing safety and efficacy in clinical trials for its drug candidates; the need to develop commercially viable drug candidates; competition from other companies, many of which are larger and better capitalized; 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 would be forced to delay, reduce, eliminate or out-license certain of its research and development programs or future commercialization efforts.

On May 5, 2015, the Company completed an initial public offering (IPO) of its common stock, which resulted in the sale of 9,367,708 shares of its common stock at a price to the public of \$18.00 per share, including 1,221,874 shares of common stock sold by the Company pursuant to the exercise in full by the underwriters of their option to purchase additional shares in connection with the offering. The Company received net proceeds of \$154.8 million, after deducting underwriting discounts and commissions and offering expenses paid by the Company.

On December 13, 2016, the Company closed its underwritten public offering of 5,750,000 shares of its common stock at a price to the public of \$25.00 per share, including 750,000 shares of common stock sold by the Company pursuant to the exercise in full by the underwriters of their option to purchase additional shares in connection with the offering. The Company received net proceeds of \$134.5 million, after deducting underwriting discounts and commissions and offering expenses paid by the Company.

On April 4, 2017, the Company closed its underwritten public offering of 5,750,000 shares of its common stock at a price to the public of \$40.00 per share, including 750,000 shares of common stock sold by the Company pursuant to the exercise in full by the underwriters of their option to purchase additional shares in connection with the offering. The Company received net proceeds of approximately \$215.6 million, after deducting underwriting discounts and commissions and offering expenses payable by the Company.

On December 15, 2017, the Company closed its underwritten public offering of 4,259,259 shares of its common stock at a price to the public of \$81.00 per share, including 555,555 shares of common stock sold by the Company pursuant to the exercise in full by the underwriters of their option to purchase additional shares in connection with the offering. The Company received net proceeds of approximately \$325.7 million, after deducting underwriting discounts and commissions and offering expenses payable by the Company.

As of December 31, 2018, the Company had cash, cash equivalents and investments of \$494.0 million. Based on the Company's current plans, the Company expects that its existing cash, cash equivalents and investments, excluding any potential option fees and milestone payments under its existing collaborations with Roche and CStone, will be sufficient to enable it to fund its operating expenses and capital expenditure requirements into the second half of 2020.

## 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 United States (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 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, and Blueprint Medicines (Switzerland) GmbH. All intercompany transactions and balances have been eliminated.

Due to the underwritten public offerings completed on December 13, 2016, April 4, 2017, and December 15, 2017, there were significant increases in shares outstanding in the years ended December 31, 2017 and 2016, which impacts the year-over-year comparability of the Company's net loss per share calculations.

### ***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, stock-based compensation expense, accrued expenses, and income taxes.

### ***Revenue Recognition***

Effective January 1, 2018, the Company adopted ASC 606, using the modified retrospective transition method. Under this method, results for reporting periods beginning after January 1, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with ASC Topic 605, *Revenue Recognition* (ASC 605). The Company only applied the modified retrospective transition method to contracts that were not completed as of January 1, 2018, the effective date of adoption for ASC 606. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity 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 entity 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.

The Company enters into licensing agreements that are within the scope of ASC 606, under which it may exclusively license rights to research, develop, manufacture and commercialize its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products.

In determining the appropriate amount of revenue to be recognized as it fulfills its obligations under its agreements, 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.

Amounts received prior to revenue recognition are recorded as deferred revenue. 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.

*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 the services are performed and presented on a gross basis because the Company is the principal for such efforts. Reimbursements from and payments to 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.

For a complete discussion of accounting for collaboration revenues, see Note 8, "Collaborations."

Prior to January 1, 2018, the Company recognized revenue from license and collaboration agreements in accordance with FASB ASC Topic 605, *Revenue Recognition* (ASC 605). Accordingly, revenue was recognized when all of the following criteria were met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria were recognized as deferred revenue in the Company's balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date were classified as deferred revenue, current portion. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date were classified as deferred revenue, net of current portion.

When evaluating multiple element arrangements, the Company considered whether the deliverables under the arrangement represented separate units of accounting. This evaluation required subjective determinations and required management to make judgments about the individual deliverables and whether such deliverables were separable from the other aspects of the contractual relationship. In determining the units of accounting, management evaluated certain criteria, including whether the deliverables have standalone value, based on the consideration of the relevant facts and circumstances for each arrangement. The consideration received was allocated among the separate units of accounting using the relative selling price method, and the applicable revenue recognition criteria were applied to each of the separate units. Deliverables were considered separate units of accounting provided that: (i) the delivered item(s) has value to the customer on a stand-alone basis and (ii) if the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in the control of the Company. In assessing whether an item had stand-alone value, the Company considered factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considered whether the collaboration partner could use the deliverable(s) for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there were other vendors that can provide the undelivered element(s). The Company's collaboration agreements with Alexion and Roche do not contain a general right of return relative to the delivered item(s).

Arrangement consideration that is fixed or determinable was allocated among the separate units of accounting using the relative selling price method. Then, the applicable revenue recognition criteria in ASC 605-25 were applied to each of the separate units of accounting in determining the appropriate period and pattern of recognition. The Company

determined the selling price of a unit of accounting following the hierarchy of evidence prescribed by ASC 605-25. Accordingly, the Company determined the estimated selling price for units of accounting within each arrangement using vendor-specific objective evidence (VSOE) of selling price, if available, third-party evidence (TPE) of selling price if VSOE is not available, or best estimate of selling price (BESP) if neither VSOE nor TPE is available. The Company typically used BESP to estimate the selling price, since it generally did not have VSOE or TPE of selling price for its units of accounting. Determining the BESP for a unit of accounting required significant judgment. In developing the BESP for a unit of accounting, the Company considered applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company validated the BESP for units of accounting by evaluating whether changes in the key assumptions used to determine the BESP would have a significant effect on the allocation of arrangement consideration between multiple units of accounting.

In the event that an element of a multiple element arrangement did not represent a separate unit of accounting, the Company recognized revenue from the combined element over the period over which it expected to fulfill its performance obligations or as undelivered items were delivered, as appropriate, if all of the other revenue recognition criteria in ASC 605-25 were met. If the pattern of performance in which the service was provided to the customer could be determined and objectively measurable performance measures existed, then the Company recognized revenue under the arrangement using the proportional performance method. If there was no discernible pattern of performance and/or objectively measurable performance measures did not exist, then the Company recognized revenue under the arrangement on a straight-line basis over the period the Company was expected to complete its performance obligations. Revenue recognized was limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method or proportional performance method, as applicable, as of the period ending date.

The Company's multiple-element revenue arrangements may include the following:

*Exclusive Licenses*

The deliverables under the Company's collaboration agreements may include exclusive licenses to research, develop, manufacture and commercialize licensed products. To account for this element of an arrangement, management evaluated whether an exclusive license had stand-alone value from the undelivered elements based on the consideration of the relevant facts and circumstances of the arrangement, including the research and development capabilities of the collaboration partner. The Company recognized the arrangement consideration allocated to licenses upon delivery of the license if facts and circumstances indicated that the license had stand-alone value from the undelivered elements, which generally included research and development services. The Company deferred arrangement consideration allocated to licenses if facts and circumstances indicated that the delivered license did not have stand-alone value from the undelivered elements.

When management believed a license did not have stand-alone value from the other deliverables to be provided in the arrangement, the Company recognized revenue attributed to the license on a proportional basis over the Company's contractual or estimated performance period, which was typically the term of the Company's research and development obligations. If management could not reasonably estimate when the Company's performance obligation ends, then revenue was deferred until management could reasonably estimate when the performance obligation ended. The periods over which revenue should be recognized were subject to estimates by management and could change over the course of the research and development and licensing agreement.

*Research and Development Services*

The deliverables 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 were recognized as the services were performed and presented on a gross basis because the Company was the principal for such efforts, so long as there was persuasive evidence of an arrangement, the fee was fixed or determinable, and collection of the related amount was reasonably assured.

### *Milestone Revenue*

The Company's collaboration agreements may include contingent milestone payments related to specified pre-clinical milestones, development milestones and sales-based commercial milestones.

At the inception of an arrangement that includes milestone payments, the Company evaluated whether each milestone was substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation included an assessment of whether:

- the consideration was commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone;
- the consideration related solely to past performance; and
- the consideration was reasonable relative to all of the deliverables and payment terms within the arrangement.

The Company evaluated factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the respective milestone and the level of effort and investment required to achieve the respective milestone in making this assessment. There was considerable judgment involved in determining whether a milestone satisfied all of the criteria required to conclude that a milestone was substantive. Milestones that were not considered substantive were accounted for as license payments and recognized over the remaining period of performance from the date of achievement of the milestone. Milestones that were considered substantive was recognized in their entirety upon successful accomplishment of the milestone with a cumulative catch up adjustments, assuming all other revenue recognition criteria were met.

### *Collaborative Arrangements*

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, generally by analogy to ASC 606. Amounts that are owed to collaboration partners are recognized as an offset to collaboration revenues as such amounts are incurred by the collaboration partner. Where amounts owed to a collaboration partner exceed the Company's collaboration revenues in each quarterly period, such amounts are classified as research and development expense. For those elements of the arrangement that are accounted for pursuant to ASC 606, the Company applies the five-step model described above under ASC 606.

For a complete discussion of accounting for collaboration revenues, see Note 8, "Collaborations."

### *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, 2018 and 2017.

#### ***Cash and cash equivalents***

The Company considers all highly liquid investments purchased with original final maturities of 90 days or less from the date of purchase to be cash equivalents. As of December 31, 2018 and December 31, 2017, cash equivalents were comprised of money market funds and other debt securities with maturities less than 90 days from the date of purchase. Cash equivalents are reported at fair value.

#### ***Available-for-Sale Investments***

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Marketable securities with a remaining maturity date greater than one year are classified as non-current. Available-for-sale securities are maintained by an investment manager and may consist of U.S. Treasury securities and U.S. government agency securities. Available-for-sale 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). If any adjustment to fair value reflects a decline in value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is "other-than-temporary" and, if so, will mark the investment to market through a charge to the Company's statement of operations and comprehensive 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 and unrealized gains and losses on investments.

#### ***Research and Development Costs***

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.

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.

### **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 through December 31, 2018.

### **Stock-Based Compensation Expense**

Stock-based compensation awards are accounted for in accordance with ASC 718, *Compensation – Stock Compensation*, or 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. Prior to 2017, expense was recognized net of estimated forfeitures and adjusted to reflect actual forfeitures. Effective January 1, 2017, upon adoption of ASU No. 2016-09, *Compensation – Stock Compensation* under the modified retrospective approach, the Company began recognizing gross stock compensation expense with actual forfeitures recognized as they occur. Compensation cost for restricted stock awards issued to employees is measured using the grant date intrinsic value of the award 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 reported volatility 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. The Company computes the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our stock-based awards. The Company intends to consistently apply this process using representative companies until a sufficient amount of historical information regarding the volatility of its own share price becomes available;
- 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;
- 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 of the intrinsic value of equity instruments issued, whichever is more reliably measured. The measurement date for non-employee awards is the date of grant without changes in the fair value of the award. 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 (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.

### ***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 the Company's subsidiary with 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.

### ***Reclassifications***

Certain items in the prior year's consolidated financial statements have been reclassified to conform to the current presentation.

### ***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 and accounts receivable.

The Company maintains its cash, cash equivalents and investments in a custodian account at high quality financial institutions, and as of December 31, 2018 and 2017, substantially all the Company's cash, cash equivalents and investments were invested in money market funds and U.S. 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 receivable represents amounts due from the Company's collaboration partners. The Company monitors economic conditions to identify facts or circumstances that may indicate that its accounts receivable is 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 United States and Switzerland.

### New Accounting Pronouncement

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.

#### Revenue recognition

In May 2014, the FASB issued Accounting Standards Update (ASU) No. 2014-09, which amends the guidance for accounting for revenue from contracts with customers. ASU No. 2014-09 superseded the revenue recognition requirements in ASC 605 and created ASC 606 described above. Effective January 1, 2018, the Company adopted ASC 606 using the modified retrospective transition method.

As a result of adopting ASC 606, the Company has recorded a cumulative-effect increase to opening accumulated deficit of \$5.3 million as of January 1, 2018 and a corresponding increase to deferred revenue primarily as a result of the treatment of the up-front consideration received from Roche in March 2016 that was recorded under ASC 605 prior to the adoption of ASC 606. A summary of the amount by which each financial statement line item was affected by the impact of the cumulative adjustment is set forth in the table below.

<b>Impact of ASC 606 Adoption on Consolidated Balance Sheet as of January 1, 2018</b>			
(in thousands)	<b>As reported under ASC 606</b>	<b>Adjustments</b>	<b>Balances without adoption of ASC 606</b>
Deferred revenue, current portion	\$ 4,478	\$ (895)	\$ 5,373
Deferred revenue, net of current portion	\$ 36,210	\$ 6,210	\$ 30,000
Accumulated deficit	\$ (360,904)	\$ (5,315)	\$ (355,589)

A summary of the amount by which each financial statement line item was affected in the current reporting period by ASC 606 as compared with the guidance that was in effect prior to the adoption of ASC 606 is set forth in the tables below.

<b>Impact of ASC 606 Adoption on Consolidated Balance Sheet as of December 31, 2018</b>			
(in thousands)	<b>As reported under ASC 606</b>	<b>Adjustments</b>	<b>Balances without adoption of ASC 606</b>
Deferred revenue, current portion	\$ 3,600	\$ (1,540)	\$ 5,140
Deferred revenue, net of current portion	\$ 42,567	\$ 17,056	\$ 25,511
Accumulated deficit	\$ (597,545)	\$ (15,516)	\$ (582,029)

<b>Impact of ASC 606 Adoption on Consolidated Statement of Operations and Comprehensive Loss for the Year Ended December 31, 2018</b>			
(in thousands)	<b>As reported under ASC 606</b>	<b>Adjustments</b>	<b>Balances without adoption of ASC 606</b>
Collaboration revenue	\$ 44,521	\$ (10,201)	\$ 54,722
Net loss	\$ (236,642)	\$ (10,201)	\$ (226,441)
Net loss per share - basic and diluted	\$ (5.39)	\$ (0.23)	\$ (5.16)

**Impact of ASC 606 Adoption on Consolidated Statement of Cash Flows for the Year Ended December 31, 2018**

(in thousands)	<b>As reported under ASC 606</b>	<b>Adjustments</b>	<b>Balances without adoption of ASC 606</b>
Net Loss	\$ (236,642)	\$ (10,201)	\$ (226,441)
Changes in deferred revenue	\$ 5,479	\$ 757	\$ 4,722

The most significant change to the Company’s accounting for revenue as a result of the adoption of ASC 606 relates to its revenue recognition pattern under step (v) above for the Company’s collaboration and license agreement with Roche (as amended, the Roche agreement). Under ASC 605, the Company was recognizing the revenue allocated to each unit of accounting on straight-line basis over the period the Company expected to complete its obligations. Under ASC 606, the Company is recognizing the revenue allocated to each performance obligation measuring progress using an input method over the period the Company expects to complete each performance obligation. ASC 606 also requires disclosure of the nature, amount, timing, and uncertainty of revenue and cash flows arising from contracts with customers. For further discussion of the adoption of this standard, see Note 8, “Collaborations.”

*Leasing*

In February 2016, the FASB issued *ASU No. 2016-02, Leases (Topic 842)*. This new standard establishes a right-of-use (ROU) model that requires all lessees to recognize ROU assets and liabilities on their balance sheet that arise from leases with terms longer than 12 months as well as provide disclosures with respect to certain qualitative and quantitative information related to their leasing arrangements. This new standard became effective for the Company on January 1, 2019.

The FASB subsequently issued the following amendments to *ASU 2016-02, Leases (Topic 842)*, which have the same effective date and transition date of January 1, 2019:

- *ASU No. 2018-10, Codification Improvements to Topic 842, Leases*, which amends certain narrow aspects of the guidance issued in ASU 2016-02; and
- *ASU No. 2018-11, Leases (Topic 842): Targeted Improvements*, which allows for a transition approach to initially apply ASU 2016-02 at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption as well as an additional practical expedient for lessors to not separate non-lease components from the associated lease component.
- *ASU No. 2018-20, Narrow-Scope Improvements for Lessors*, which contains certain narrow scope improvements to the guidance issued in ASU 2016-02

The Company elected to adopt the new leasing standards using a modified retrospective transition approach to be applied to leases existing as of, or entered into after, January 1, 2019. The Company also elected the “package of practical expedients”, which permits the Company not to reassess under the new standards for prior conclusions about lease identification, lease classification and initial direct costs. The Company is continuing to assess its existing lease contracts, finalize the calculations, including discount rate assumptions, to evaluate the impact that the new leasing standards may have on its consolidated results of operations, financial position and disclosures. The Company is also continuing to establish new processes and internal controls that may be required to comply with the new lease accounting and disclosure requirements set by the new standard. The Company expects that the adoption of the new leasing standards will result in the recognition of material ROU assets and liabilities in its consolidated balance sheets. The Company does not expect the adoption of the new leasing standards will have a material impact to its consolidated statements of income.

### *Credit Losses*

In June 2016, the FASB issued *ASU No. 2016-13, Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*. This standard requires that credit losses be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. This standard will be effective for the Company on January 1, 2020. The Company is currently evaluating the potential impact that this standard may have on its consolidated financial position and results of operations.

### *Debt Securities*

In March 2017, the FASB issued *ASU No. 2017-08, Receivables - Nonrefundable Fees and Other Costs (Subtopic 310-20): Premium Amortization on Purchased Callable Debt Securities*. This standard amends the amortization period for certain purchased callable debt securities held at a premium by shortening the amortization period to the earliest call date. This standard became effective for the Company on January 1, 2019, and was adopted using a modified retrospective transition approach. Based upon the Company's marketable debt securities held as of December 31, 2018, the adoption of this standard did not result in a significant adjustment to the Company's marketable debt securities.

### *Fair Value Measurements*

In August 2018, the FASB issued *ASU No. 2018-13, Fair Value Measurement (Topic 820): Disclosure Framework Changes to the Disclosure Requirements for Fair Value Measurement*. This standard modifies certain disclosure requirements on fair value measurements. This standard will be effective for the Company on January 1, 2020. The Company does not expect that the adoption of this standard will have a material impact on the disclosures.

### *Collaborative Arrangements*

In November 2018, the FASB issued *ASU No. 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*. This standard makes targeted improvements for collaborative arrangements as follows:

- Clarifies that certain transactions between collaborative arrangement participants should be accounted for as revenue under *ASC 606, Revenue from Contracts with Customers*, when the collaborative arrangement participant is a customer in the context of a unit of account. In those situations, all the guidance in *ASC 606* should be applied, including recognition, measurement, presentation and disclosure requirements;
- Adds unit-of-account guidance to *ASC 808, Collaborative Arrangements*, to align with the guidance in *ASC 606* (that is, a distinct good or service) when an entity is assessing whether the collaborative arrangement or a part of the arrangement is within the scope of *ASC 606*; and
- Requires that in a transaction with a collaborative arrangement participant that is not directly related to sales to third parties, presenting that transaction together with revenue recognized under *ASC 606* is precluded if the collaborative arrangement participant is not a customer.

This standard will be effective for the Company on January 1, 2020; however, early adoption is permitted. A retrospective transition approach is required for either all contracts or only for contracts that are not completed at the date of initial application of *ASC 606*, with a cumulative adjustment to opening retained earnings. The Company is currently evaluating the potential impact that this standard may have on its consolidated financial position and results of operations.

### *Internal-Use Software*

In August 2018, the FASB issued *ASU No. 2018-15, Intangibles-Goodwill and Other-Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That*

Is a Service Contract, which clarifies the accounting for implementation costs in cloud computing arrangements. This standard will be effective for the Company on January 1, 2020, however, early adoption is permitted. The Company currently is evaluating the impact the adoption may have on its consolidated financial position and results of operations.

#### Statement of Cash Flows: Restricted Cash

In November 2016, the FASB issued ASU 2016-18, *Statement of Cash Flows: Restricted Cash*, which requires that amounts generally described as restricted cash and restricted cash equivalents be included within cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This standard became effective on January 1, 2018 and is effective on a retrospective basis. The adoption of this new standard did not have a material impact on the Company's consolidated financial position, results of operations or statement of cash flows; however, it has resulted in the reclassification of certain prior year amounts in the Company's consolidated statements of cash flows to conform to current year presentation.

### 3. Cash Equivalents and Investments

Cash equivalents and investments, available-for-sale, consisted of the following at December 31, 2018 and December 31, 2017 (in thousands):

	Amortized Cost	Unrealized Gain	Unrealized Losses	Fair Value
<b>December 31, 2018</b>				
Cash equivalents:				
Money market funds	\$ 68,064	\$ —	\$ —	\$ 68,064
Investments, available-for-sale:				
U.S. treasury obligations	426,112	—	(164)	425,948
<b>Total</b>	<b>\$ 494,176</b>	<b>\$ —</b>	<b>\$ (164)</b>	<b>\$ 494,012</b>
	Amortized Cost	Unrealized Gain	Unrealized Losses	Fair Value
<b>December 31, 2017</b>				
Cash equivalents:				
Money market funds	\$ 400,304	\$ —	\$ —	\$ 400,304
Investments, available-for-sale:				
U.S. treasury obligations	273,321	—	(269)	273,052
<b>Total</b>	<b>\$ 673,625</b>	<b>\$ —</b>	<b>\$ (269)</b>	<b>\$ 673,356</b>

The cost of securities sold is determined based on the specific identification method for purposes of recording realized gains and losses. During the years ended December 31, 2018 and 2017, there were no realized gains or losses on sales of investments, and no investments were adjusted for other than temporary declines in fair value.

At December 31, 2018 and 2017, the Company held 54 and 37 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, 2018 and 2017 were \$397.5 million and \$273.1 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. The Company determined that there was no material change in the credit risk of the above investments. As a result, the Company determined it did not hold any investments with an other-than-temporary impairment as of December 31, 2018 and December 31, 2017.

No available-for-sale securities held as of December 31, 2018 or December 31, 2017 had remaining maturities greater than one year.

#### 4. Fair Value of Financial Instruments

The following table summarizes our cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2018 (in thousands):

Description	December 31, 2018	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
<b>Financial Assets</b>				
Cash equivalents:				
Money market funds	\$ 68,064	\$ 68,064	\$ —	\$ —
Investments, available-for-sale:				
U.S Treasury obligations	425,948	425,948	—	—
<b>Total</b>	<b>\$ 494,012</b>	<b>\$ 494,012</b>	<b>\$ —</b>	<b>\$ —</b>

The following table summarizes our cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2017 (in thousands):

Description	December 31, 2017	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
<b>Financial Assets</b>				
Cash equivalents:				
Money market funds	\$ 400,304	\$ 400,304	\$ —	\$ —
Investments, available-for-sale:				
U.S Treasury obligations	273,052	273,052	—	—
<b>Total</b>	<b>\$ 673,356</b>	<b>\$ 673,356</b>	<b>\$ —</b>	<b>\$ —</b>

At December 31, 2017, the fair value of the Company's term loan payable was determined using current applicable rates for similar instruments as of the balance sheet date. The carrying value of the Company's term loan payable approximated fair value because the Company's interest rate yield approximated current market rates. The Company's term loan payable was a Level 3 liability within the fair value hierarchy.

#### 5. Restricted Cash

At December 31, 2018 and December 31, 2017, \$5.4 million and \$4.8 million, respectively, of the Company's cash is restricted by a bank related to security deposits for the lease agreements for the Company's current and former corporate headquarters.

For additional information on these security deposits, see Note 14, *Commitments*

#### 6. Property and Equipment, Net

Property and equipment and related accumulated depreciation are as follows (in thousands):

	Estimated Useful Life (Years)	December 31, 2018	December 31, 2017
Lab equipment	5	\$ 6,232	\$ 3,604
Furniture and fixtures	4	2,369	837
Computer equipment	3	1,805	624
Leasehold improvements	Term of lease	26,640	4,681
Software	3	280	263
Construction-in-progress		956	18,998
		38,282	29,007
Less: accumulated depreciation and amortization		(8,655)	(4,644)
<b>Total property and equipment, net</b>		<b>\$ 29,627</b>	<b>\$ 24,363</b>

Depreciation expense for the years ended December 31, 2018, 2017 and 2016 was \$4.2 million, \$1.6 million and \$1.6 million, respectively.

## 7. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	<u>December 31,</u> <u>2018</u>	<u>December 31,</u> <u>2017</u>
External research and development	\$ 36,213	\$ 17,493
Employee compensation	8,071	5,766
Accrued professional fees	3,379	1,394
Property and equipment costs	912	4,176
Pre-commercial accrual	1,044	261
Other	2,092	1,451
	<u>\$ 51,711</u>	<u>\$ 30,541</u>

## 8. Collaborations

### *CStone Pharmaceuticals*

On June 1, 2018, the Company entered into a Collaboration and License Agreement (the CStone agreement) with CStone pursuant to which the Company granted CStone exclusive rights to develop and commercialize the Company's drug candidates BLU-554, avapritinib and BLU-667, 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 will retain exclusive rights to the licensed products outside the CStone territory.

The Company received an upfront cash payment of \$40.0 million, and subject to the terms of the CStone agreement, will be eligible to receive up to approximately \$346.0 million in milestone payments, including \$118.5 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 BLU-554 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 will be responsible for conducting all development and commercialization activities in the CStone territory related to the licensed products, and the Company and CStone plan to conduct a proof-of-concept clinical trial in China evaluating BLU-554 in combination with CS1001, a clinical stage anti-programmed death ligand-1 immunotherapy being developed by CStone, as a first-line therapy for the treatment of patients with hepatocellular carcinoma.

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 after June 1, 2019, 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. Accordingly, the Company recorded a reduction of expenses of \$0.5 million for the year ended December 31, 2018.

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 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 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. There was no adjustment in the transaction price as of December 31, 2018. Because the performance obligations have been satisfied, any addition to the transaction price would be immediately recognized as revenue.

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 second quarter of 2018, and there was no revenue deferred as a contract liability associated with the CStone agreement as of December 31, 2018.

### **Roche**

In March 2016, the Company entered into a collaboration and license agreement (as amended, Roche agreement) with Roche for the discovery, development and commercialization of up to five small molecule therapeutics targeting kinases believed to be important in cancer immunotherapy, as single products or possibly in combination with other therapeutics. The parties are currently conducting activities for up to five programs under the collaboration, including up to two collaboration programs leveraging the Company's novel target discovery engine and proprietary compound library to select potential targets.

Under the Roche agreement, Roche is 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. For up to three of the five collaboration programs, if Roche exercises its option, Roche will receive worldwide, exclusive commercialization rights for the licensed products. For up to two of the five collaboration programs, if Roche exercises its option, the Company will retain commercialization rights in the United States for the licensed products, and Roche will receive commercialization rights outside of the United States for the licensed products. 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 pre-clinical 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 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 United States.

The Company received an upfront cash payment of \$45.0 million in March 2016 upon execution of the Roche agreement, and subject to the terms of the Roche agreement, the Company will be eligible to receive up to approximately \$965.0 million in contingent option fees and milestone payments related to specified research, pre-clinical, clinical, regulatory and sales-based milestones. Of the total contingent payments, up to approximately \$215.0 million are for option fees and milestone payments for research, pre-clinical and clinical development events prior to licensing across all five potential collaboration programs, including contingent milestone payments for initiation of each of the collaboration programs for which the parties will work together to select targets (pre-option exercise milestones). In June 2018, the Company achieved and received a \$10.0 million research milestone payment. 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 United States, 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 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 agreement. Prior to its exercise of its first option, Roche may terminate the Roche 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 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 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 products 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 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 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.

In June 2018, the Company achieved and received a \$10.0 million research milestone payment related to the Roche agreement, and it became probable that a significant reversal of cumulative revenue would not occur for the \$10.0 million research milestone achieved. At such time, the associated consideration was added to the estimated transaction price and allocated to the existing performance obligation. The Company recognized a cumulative catch-up of \$1.2 million to revenue for this developmental milestone during the second quarter of 2018, representing the amount that would have been recognized had the milestone payment been included in the transaction price from the outset of the arrangement.

The Company recognized 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.

During the year ended 2018, there has been no significant changes in the costs expected to be incurred in the future to satisfy the performance obligation, and the Company recognized revenue of \$4.5 million under the Roche collaboration, of which \$2.9 million was recognized as a result of the change in the contract liability balances as of January 1, 2018. As of December 31, 2018, the Company had revenue deferred as a contract liability related to the

Roche agreement of \$46.2 million, of which \$3.6 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 six years.

Prior to January 1, 2018, the Company recognized revenue in accordance with ASC 605. The Company determined that there were five deliverables under the Roche collaboration: (i) a non-transferable, sub-licensable and non-exclusive license to use the Company's intellectual property and collaboration compounds to conduct research activities; (ii) conducting research and development activities through Phase 1 clinical trials under the research plan; (iii) providing pre-clinical and clinical supply of collaboration compounds; (iv) participation on a joint research committee (JRC) and joint development committee (JDC); and (v) regulatory responsibilities under Phase 1 clinical trials.

The Company determined that the license did not have value to Roche on a stand-alone basis due to the specialized nature of the research activities to be provided by the Company that are not available in the marketplace and the fact that the license is to perform research and development only. Therefore, the license has limited value without the performance of the research and development activities and is not separable. The pre-clinical and clinical supply activities are integral to the performance of the research and development activities and can only be used for the performance of such activities, and the regulatory responsibilities are dependent on the research and development activities. The Company determined that the best estimate for the selling price of the JRC and JDC participation was inconsequential. Accordingly, the Company combined the license, pre-clinical and clinical supply, JRC and JDC participation and regulatory responsibilities deliverables with the research and development activities, the last item to be delivered in the arrangement, as one unit of accounting. The Company is recognizing the total allocable arrangement consideration consisting of the upfront payment of \$45.0 million as revenue on a straight-line basis over the Company's best estimate of the period it expects to perform research and development activities.

The Company evaluated whether the option fees that may be received in connection with the Roche agreement are substantive. The Company concluded that the option fees were substantive due to the uncertainty around whether the goals of the collaboration would be achieved, and therefore the options were not a deliverable in the current arrangement. If Roche elects to exercise the options, the exercises and related contingent deliverables would be accounted for as a separate arrangement.

The Company evaluated whether the milestones that may be received in connection with the Roche agreement are substantive milestones. Pre-option exercise milestones that are expected to be achieved as a result of the Company's efforts during the performance of the research and development activities were considered substantive and would be recognized as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. The development event milestones were not considered substantive because the Company does not contribute effort to the achievement of such milestones as they are expected to be achieved after the performance of the research and development activities. Consideration received with respect to these milestones would be added to the total arrangement consideration that has been allocated to the identified units of accounting. There were no milestones achieved prior to the adoption of ASC 606 on January 1, 2018.

During the years ended 2017 and 2016, the Company recognized revenue under the Roche collaboration of \$5.2 million and \$4.5 million, respectively, which represented a portion of the \$45.0 million upfront payment.

### ***Alexion***

In March 2015, the Company entered into a research, development and commercialization agreement (Alexion agreement) with Alexion to research, develop and commercialize one or more drug candidates targeting the ALK2 kinase for the treatment of fibrodysplasia ossificans progressiva (FOP). On July 26, 2017, the Company received written notice from Alexion of its election to terminate the Alexion agreement for convenience, and the termination became effective on October 24, 2017. Since the Alexion agreement terminated prior to January 1, 2018, the Company recognized revenue from the Alexion collaboration in accordance with ASC 605.

Pursuant to the Alexion agreement, the Company was responsible for research and pre-clinical development activities related to any drug candidates, and Alexion was responsible for all clinical development, manufacturing and commercialization activities related to any drug candidates. In addition, Alexion was responsible for funding 100% of the Company's research and development costs incurred under the research plan, including pass through costs and a negotiated yearly rate per full time equivalent for its employees' time and their associated overhead expenses. Prior to

the termination, the Company had received an aggregate amount of \$18.8 million in upfront and milestone payments, which consist of a \$15.0 million non-refundable upfront payment in March 2015 upon execution of the Alexion agreement and an aggregate amount of \$3.8 million in pre-clinical milestone payments. As a result of the termination of the Alexion agreement, the Company was not entitled to receive payment from Alexion for any research and development expenses incurred after the effective date of termination.

The Company determined that there were three deliverables under the former Alexion collaboration: (i) an exclusive license to research, develop, manufacture and commercialize the licensed products and the compounds in the field in the territory, (ii) conducting research and development activities under the research plan and (iii) participation on a joint steering committee (JSC) and joint project team (JPT).

The Company determined that the license did not have value to Alexion on a stand-alone basis due to the specialized nature of the research services to be provided by the Company that are not available in the marketplace. Therefore, the deliverables were not separable and, accordingly, the license, undelivered research and development activities and JSC and JPT participation were a single unit of accounting. The Company recognized revenue for the \$15.0 million upfront payment and a \$1.8 million non-substantive milestone payment utilizing the proportional performance model over the period of performance, which ended October 24, 2017, and recognized revenue for the remaining \$2.0 million substantive milestone payments upon achievement.

As a result of the termination, the Company did not recognize revenue under the Alexion agreement for the year ended December 31, 2018. During the year ended December 31, 2017, the Company recognized revenue under the former Alexion collaboration of \$16.2 million, which represents \$9.5 million of reimbursable research and development costs, as well as a portion of the \$15.0 million upfront payment and the \$1.8 million non-substantive milestone payment previously received. During the year ended December 31, 2016, the Company recognized revenue under the Alexion agreement of \$23.3 million, which represents \$14.6 million of reimbursable research and development costs, \$1.8 million in milestone payments that were recognized upon achievement, as well as a portion of the \$15.0 million upfront payment and the \$1.8 million non-substantive milestone payment previously received.

During the year ended December 31, 2017, the Company received \$12.7 million related to reimbursable research and development costs under the former Alexion collaboration.

## **9. Term Loan**

In May 2013, the Company entered into a loan and security agreement with Silicon Valley Bank, which provided for up to \$5.0 million in funding, to be made available in three tranches. Loan advances accrue interest at a fixed rate of 2% above the prime rate. In November 2014, the Company amended the loan to allow the Company to borrow an additional \$5.0 million. The Company accounted for the amendment as a modification to the existing 2013 loan. The Company immediately drew the additional \$5.0 million and was required to make interest-only payments until December 1, 2015, and consecutive monthly payments of principal, plus accrued interest, over the remaining term through November 2018. The Company was required to pay a fee of 4% of the total loan advances at the end of the term of each of the loan. The fee had been accreted to interest expense over the term of the loan. As of December 31, 2018, the Company had no outstanding principal and interest under the loan and security agreement.

## **10. Stock-based compensations**

### ***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 share 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 year beginning January 1, 2018 and 2019, the number of shares reserved for issuance under the 2015 Plan was increased by 1,743,101 and 1,761,481 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 our capitalization. At December 31, 2018, there were 1,776,005 shares available for future grant under the 2015 Plan.

### **Stock-based compensation expense**

The Company recognized stock-based compensation expense totaling \$30.5 million, \$12.5 million and \$6.1 million for the year ended December 31, 2018, 2017 and 2016, respectively.

Stock-based compensation expense by award type included within the consolidated statements of operations and comprehensive loss was as follows (in thousands):

	Year Ended December 31,		
	2018	2017	2016
Stock options	\$ 30,095	\$ 12,317	\$ 5,134
Restricted stock units	167	—	—
Restricted stock awards	—	2	839
Employee stock purchase plan	272	204	167
Total stock-based compensation expense	<u>\$ 30,534</u>	<u>\$ 12,523</u>	<u>\$ 6,140</u>

Stock-based compensation expense by classification within the consolidated statements of operations and comprehensive loss is as follows (in thousands):

	Year Ended December 31,		
	2018	2017	2016
Research and development	\$ 17,019	\$ 6,296	\$ 2,674
General and administrative	13,515	6,227	3,466
Total stock-based compensation expense	<u>\$ 30,534</u>	<u>\$ 12,523</u>	<u>\$ 6,140</u>

At December 31, 2018, there was \$93.2 million of total unrecognized compensation cost related to non-vested stock awards, which is expected to be recognized over a weighted-average period of 2.8 years. Due to an operating loss, the Company does not record tax benefits associated with stock-based compensation or option exercises. Tax benefit will be recorded when realized.

### **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, 2018	December 31, 2017	December 31, 2016
Risk-free interest rate	2.77 %	2.07 %	1.55 %
Expected dividend yield	— %	— %	— %
Expected term (years)	6.0	6.0	6.0
Expected stock price volatility	69.08 %	74.58 %	75.94 %

The following table summarizes the stock option activity for the year ended December 31, 2018:

	Shares	Weighted-Average Exercise Price	Remaining Contractual Life (in Years)	Aggregate Intrinsic Value(1) (in thousands)
Outstanding at December 31, 2017	3,304,166	\$ 22.45	8.04	\$ 174,985
Granted	1,832,270	77.64		
Exercised	(445,622)	12.54		
Canceled	(133,014)	55.65		
Outstanding at December 31, 2018	4,557,800	\$ 44.64	7.96	\$ 86,675
Exercisable at December 31, 2018	2,103,540	\$ 24.32	6.97	\$ 68,641

- (1) Intrinsic value represents the amount by which the fair market value as of December 31, 2018 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, 2018, 2017 and 2016 was \$49.40, \$28.04 and \$13.06, respectively. The total intrinsic value of options exercised in the years ended December 31, 2018, 2017, and 2016 was \$29.4 million, \$17.8 million and \$3.1 million, respectively.

At December 31, 2018, the total unrecognized compensation expense related to unvested stock option awards was \$90.9 million, which is expected to be recognized over a weighted-average period of approximately 2.7 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, 2018:

	Shares	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2017	—	\$ —
Granted	36,868	66.28
Vested	—	—
Forfeited	—	—
Unvested shares at December 31, 2018	36,868	66.28

No restricted stock units vested during the years ended December 31, 2018, 2017 and 2016. At December 31, 2018, the total unrecognized compensation expense related to unvested restricted stock units was \$2.3 million, which we expect to recognize over a weighted-average period of approximately 3.7 years.

### Restricted stock awards

Restricted stock awards granted by the Company generally vest ratably over four years. The Company did not grant restricted stock awards to any employees or directors during the years ended December 31, 2018 or 2017. Outstanding restricted stock awards previously granted to employees and directors were fully vested as of December 31, 2017. The total fair value of restricted stock awards that vested during the years ended December 31, 2017 and 2016 was \$0.1 million and \$2.7 million, respectively.

### 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 year beginning January 1, 2018 and 2019, the

number of shares reserved for issuance under the 2015 ESPP was increased by 435,775 and 440,370 shares, respectively. The Company issued 13,878, 16,703 and 23,325 shares under the ESPP during the years ended 2018, 2017 and 2016 respectively.

## 11. Net Loss per Share

Basic net loss per share is calculated by dividing net loss by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net 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 dilutive net loss per share calculation, stock options, unvested restricted stock units and ESPP shares are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive; therefore, basic and diluted net loss per share were the same for all periods presented as a result of the Company's net loss.

The following common stock equivalents were excluded from the calculation of diluted net loss per share for the periods indicated because including them would have had an anti-dilutive effect.

	Year Ended December 31,		
	2018	2017	2016
Stock options	4,557,800	3,304,166	2,622,741
Restricted stock units	36,868	—	—
Restricted stock awards	—	—	2,125
ESPP shares	10,275	5,663	7,798
Total	4,604,943	3,309,829	2,632,664

The weighted average number of common shares used in net loss per share on a basic and diluted basis were 43,867,433, 37,792,929 and 27,491,669 for the years ended December 31, 2018, 2017 and 2016, respectively.

## 12. Convertible Preferred Stock

Upon the closing of the IPO in May 2015, Series A Convertible Preferred Stock, Series B Convertible Preferred Stock and Series C Convertible Preferred Stock automatically converted into 15,467,479 shares of common stock. In addition, upon closing of the IPO, the Company's board of directors was authorized, without action by the stockholders, to designate and issue up to an aggregate of 5,000,000 shares of preferred stock in one or more series. The board of directors can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. No shares of preferred stock were issued and outstanding during 2018, 2017 and 2016.

## 13. 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, 2018, 2017 and 2016

	Year Ended December 31,		
	2018	2017	2016
Federal income tax (benefit) at statutory rate	21.00 %	34.00 %	34.00 %
Permanent differences	1.71	0.49	(2.74)
Federal research and development credits	1.79	0.97	1.02
Federal orphan drug credits	18.06	6.40	6.63
State income tax, net of federal benefit	7.08	5.40	4.81
Other	0.04	0.83	(0.78)
Deferred rate change	—	(27.58)	—
Change in valuation allowance	(49.68)	(20.54)	(42.94)
Effective income tax rate	— %	(0.03) %	— %

The Company had net losses in all periods presented and therefore has not recognized any federal or state income tax expense.

During 2018, the Company completed a detailed study of its R&D credits and Orphan Drug Credit carryforwards. As a result, the Company adjusted its deferred tax asset balances and the impacts are included on the Federal research and developmental credit and Federal orphan drug credit lines in the effective rate reconciliation above. The impacts of the increases in the deferred tax asset balances have been completely offset by an increase in the Company's valuation allowance which is included in the change in valuation allowance line on the reconciliation above.

The Company's deferred tax assets and liabilities consist of the following:

	Year Ended December 31,		
	2018	2017	2016
Deferred tax assets:			
Net operating loss carryforwards	\$ 127,421	\$ 78,829	\$ 69,443
Research and development credit carryforwards	13,714	5,950	3,833
Orphan drug credit carryforwards	68,536	14,574	5,095
Accrued expenses and other	12,248	4,660	2,914
Deferred revenue	10,320	9,664	2,627
Deferred lease incentive	3,993	4,462	1,324
Deferred rent	1,436	1,142	366
Total gross deferred tax asset	237,668	119,281	85,602
Deferred tax liability	(4,162)	(4,801)	(1,535)
Debt discount	—	(2)	(14)
Valuation allowance	(233,506)	(114,478)	(84,053)
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 federal and state deferred tax assets, and as a result, a valuation allowance of \$233.5 million, \$114.5 million and \$84.1 million has been established at December 31, 2018, 2017 and 2016, respectively. The change in the valuation allowance was \$119.0 million, \$30.4 million and \$31.1 million for the years ended December 31, 2018, 2017 and 2016, respectively. The Company has incurred net operating losses (NOL) since inception. At December 31, 2018, the Company had federal and state NOL carryforwards of \$464.9 million and \$471.3 million, respectively, which expire beginning in 2030. As of December 31, 2018, the Company had federal and state research and development tax credit carryforwards of \$8.5 million and \$6.2 million, respectively, which expire beginning in 2029. As of December 31, 2018, the Company had federal orphan drug credits of \$68.5 million, which expire beginning in 2035 and state investment tax credits of \$0.5 million, which expire beginning in 2018.

The Internal Revenue Code of 1986, as amended (the Code), provides for a limitation of the annual use of net operating losses 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. At this time, 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 the Company's formation. The Company may have experienced ownership changes, as defined by the Code, as a result of past financing transactions. Accordingly, the Company's ability to utilize the aforementioned carryforwards may be limited. 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.

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, 2018 and December 31, 2017, the Company has no accrued interest related to uncertain tax positions. In many cases, the Company's uncertain tax positions are related to years that remain subject to examination by relevant tax authorities. 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.

On December 22, 2017, H.R.1, known as the Tax Cuts and Jobs Act, was enacted. This new law did not have a significant impact on the Company's consolidated financial statements for the year ended December 31, 2017 because it maintains a valuation allowance on the majority of its net operating losses and other deferred tax assets. However, the reduction of the U.S. federal corporate tax rate from 35% to 21% resulted in increases to the amounts reflected in "Deferred rate change" in the Company's tax reconciliation table above for the year ended December 31, 2017 compared to the year ended December 31, 2016. The change in the U.S. federal corporate tax rate, which was effective January 1, 2018, was also reflected in the Company's deferred tax table above.

As permitted by SEC Staff Accounting Bulletin 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act, we recorded provisional estimates during the year ended December 31, 2017, and have subsequently finalized our accounting analysis based on the guidance, interpretations, and data available as of December 31, 2018. Adjustments made in the fourth quarter of 2018 upon finalization of our accounting analysis were not material to the Company's consolidated financial statements.

#### **14. Commitments**

##### *38 Sidney Street*

On February 12, 2015, the Company entered into a lease for approximately 38,500 rentable square feet of office and laboratory space at 38 Sidney Street in Cambridge, Massachusetts, which the Company gained control over on June 15, 2015, and occupancy commenced in October 2015. The initial term of the lease agreement will expire on October 31, 2022, unless terminated sooner. The Company has an option to extend the lease for five additional years. The lease has a total commitment of \$17.8 million over the initial seven-year term. The Company has agreed to pay an initial annual base rent of approximately \$2.3 million, which rises periodically until it reaches approximately \$2.8 million. The Company is recording rent expense on a straight-line basis through the end of the lease term and deferred rent on the consolidated balance sheet accordingly. The lease provided the Company with an allowance for leasehold improvements of \$4.3 million. The Company accounts for leasehold improvement incentives as a reduction to rent expense ratably over the lease term and the balance from the leasehold improvement incentives is included in lease incentive obligations on the balance sheet. The lease agreement required the Company to pay a security deposit of \$1.3 million, of which \$0.2 million was released in February 2018. The remaining \$1.1 million is recorded in restricted cash on the Company's balance sheet as of December 31, 2018.

In the first quarter of 2018, the Company subleased its former corporate headquarters at 38 Sidney Street, Cambridge, Massachusetts through October 31, 2020. Subject to the terms of the sublease agreement and the master lease agreement, including a right of recapture by the Company, the sublessee has the option to extend the sublease through October 31, 2022. The sublease includes a total commitment by the sublessee of \$8.2 million over the 32-month term of the sublease agreement. During the 32-month term, the Company will be responsible for total rental payments of \$6.9 million and an additional \$0.7 million in total payments related to the Company's profit on the sublease income which are payable by the Company to the landlord. As of December 31, 2018, the minimum sublease rental commitment by the sublessee was \$5.7 million.

##### *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. The initial term of the lease agreement commenced on October 1, 2017 and 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.

During the initial term of the lease agreement, the Company has agreed to pay 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 is recording rent expense on a straight-line basis through the end of the lease term and deferred rent on the consolidated balance sheet accordingly. The lease provided the Company with a tenant improvement allowance of approximately \$14.2 million for improvements to be made to the premises. The Company accounts for leasehold improvement incentives as a reduction to rent expense ratably over the lease term and the balance from the leasehold improvement incentives is included in lease incentive obligations on the balance sheet. The lease agreement

required the Company to pay a security deposit of \$3.5 million, which is recorded in restricted cash on the Company's balance sheet.

On September 19, 2018, the Company entered into an amendment to the lease agreement for its office and laboratory space located at 45 Sidney Street in Cambridge, Massachusetts to expand the rentable square footage from approximately 99,833 square feet to approximately 139,216 square feet. The initial term of the lease with respect to the expansion premises will commence on March 1, 2019 and will expire on November 30, 2029, unless terminated sooner. Pursuant to the lease amendment, the date on which the Company will become responsible for paying rent with respect to the expansion space will be the earlier of (i) the date upon which the Company first occupies the expansion premises for business purposes or (ii) July 1, 2019. The Company currently anticipates the rent commencement date for the expansion premises will be approximately July 1, 2019.

The Company has 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. Pursuant to the lease amendment, the landlord has also agreed to provide the Company with a tenant improvement allowance of approximately \$3.2 million for improvements to be made to the expansion premises. The lease amendment required the Company to pay an additional security deposit of \$0.8 million to the landlord for the expansion premises, which is recorded in restricted cash on the Company's balance sheet as of December 31, 2018.

The future minimum lease payments through 2023 and thereafter under non-cancellable operating leases as of December 31, 2018 (including the expansion premises) are as follows (in thousands):

2019	12,909
2020	14,926
2021	15,349
2022	15,304
2023	13,331
Thereafter	88,273
<b>Total minimum lease payments (1)</b>	<b>\$ 160,092</b>

- (1) Minimum lease payments have not been reduced by minimum sublease rentals of \$5.7 million due in the future under our non-cancelable sublease for the office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

The Company records rent expense under its lease agreements on a straight-line basis. For the years ended December 31, 2018, 2017, and 2016, rent expense, net of sublease income, was \$7.3 million, \$6.3 million, and \$1.8 million, respectively.

#### 15. Defined Contribution Benefit 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 Internal Revenue Service Code of 1986, as amended, so that contributions to the 401(k) Plan by employees or by the Company, and the investment earnings thereon, 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. Effective September 1, 2015, the Company instituted an employer match of 50% of eligible contributions up to 6% of employee contributions. For the years ended December 31, 2018, 2017 and 2016, the Company contributed \$0.8 million, \$0.5 million and \$0.4 million, respectively, to the 401(k) Plan.

#### 16. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information for 2018 and 2017. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information

for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	Three Months Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(in thousands, except per share data)			
Total revenue	\$ 954	\$ 41,439	\$ 1,095	\$ 1,033
Total operating expenses	59,865	70,906	76,603	84,175
Total other income (expense), net	2,362	2,419	2,785	2,820
Net loss	\$ (56,549)	\$ (27,048)	\$ (72,723)	\$ (80,322)
Net loss per share — basic and diluted	\$ (1.29)	\$ (0.62)	\$ (1.66)	\$ (1.83)

	Three Months Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	(in thousands, except per share data)			
Total revenue	\$ 5,840	\$ 5,890	\$ 8,068	\$ 1,628
Total operating expenses	34,170	40,104	46,678	51,721
Total other expense, net	353	802	907	1,066
Net loss	\$ (27,977)	\$ (33,412)	\$ (37,703)	\$ (49,027)
Net loss per share — basic and diluted	\$ (0.84)	\$ (0.86)	\$ (0.96)	\$ (1.23)

## 17. Subsequent Events

On February 25, 2019, the Company entered into a fourth amendment to its collaboration and license agreement, as amended, with Roche, pursuant to which the Company and Roche agreed to modify certain time periods related to Roche's option rights for one of the collaboration programs and to modify certain time periods related to the screening activities under the collaboration.

[\*\*\*] INDICATES MATERIAL THAT HAS BEEN OMITTED AND FOR WHICH CONFIDENTIAL TREATMENT HAS BEEN REQUESTED. ALL SUCH OMITTED MATERIAL HAS BEEN FILED WITH THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO RULE 24b-2 PROMULGATED UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED.

#### FOURTH AMENDMENT TO COLLABORATION AND LICENSE AGREEMENT

This Fourth Amendment (this “**Amendment**”), effective February 25, 2019 (“**Fourth Amendment Effective Date**”), is by and between F. Hoffmann-La Roche Ltd, with an office and place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland and Hoffmann-La Roche Inc., with an office and place of business at 150 Clove Road, Suite 8, Little Falls, New Jersey 07424, U.S.A. (together referred to as “**Roche**”) and Blueprint Medicines Corporation, located at 45 Sidney Street, Cambridge, Massachusetts 02139 U.S.A. (“**BPM**”). Capitalized terms used and not otherwise defined in this Amendment shall have the meanings set forth in the Agreement.

WHEREAS, BPM and Roche entered into a Collaboration and License Agreement, dated March 14, 2016, as amended by an amendment, effective April 15, 2016, a second amendment, effective April 27, 2016, and a third amendment, effective August 4, 2016 (collectively, the “**Agreement**”); and

WHEREAS, BPM and Roche desire to amend certain terms under the Agreement, as set forth below;

NOW THEREFORE, Roche and Blueprint hereby agree as follows:

1. Section 1.86 (Option Period) of the Agreement shall be deleted in its entirety and replaced by the following:

“The term ‘Option Period’ shall mean, for each Collaboration Target, the period beginning the date the MTD for the first Product for such Collaboration Target is designated by the JDC and ending upon the earliest of (i) the date that such Collaboration Target becomes a Leftover Target, (ii) [\*\*\*] after Roche’s receipt of the Option Data Package for such Collaboration Target, (iii) the date such Collaboration Target becomes a Terminated Target, (iv) the date upon which a Product (including Backup Compounds) for such Collaboration Target is no longer in GLP Tox Studies, in Phase I Studies, or progressing from GLP Tox Studies to Phase I Studies, or (v) [\*\*\*] after achievement of Lead Series Identified Criteria has been confirmed by the JRC for such Collaboration Target if Initiation of the GLP Tox Study has not been achieved for such Collaboration Target prior to such date; *provided, however*, that [\*\*\*] for purposes of this clause 1.86(v), [\*\*\*]; *provided further* that (1) in the event that the JRC [\*\*\*], then (A) [\*\*\*] and (B) [\*\*\*]; and (2) in the event that (A) the JRC [\*\*\*] and (B) if the JRC [\*\*\*], then [\*\*\*].”

2. The first sentence of Section 4.1.6 of the Agreement shall be deleted in its entirety and replaced by the following:

“Part 2 shall start with Screening of Library Compounds selected by both Parties (e.g., the diversity set comprised in BPM Technology) in both assays performed by BPM (Jurkat-cell based) and by Roche ([\*\*\*]), and the screening and validation phase of Part 2 shall end on the earlier of [\*\*\*].”

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3. Pursuant to Section 21.13 of the Agreement, the notice address for Blueprint shall be deleted and replaced with the following:

if to BPM, to: Blueprint Medicines Corporation  
45 Sidney Street  
Cambridge, Massachusetts 02139  
U.S.A.  
Attn: Legal Department

This Amendment may be executed in two (2) or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Counterparts may be delivered via facsimile, electronic mail (including pdf or other electronic signature) or other transmission method and any counterpart so delivered shall be deemed to have been duly and validly delivered and be valid and effective for all purposes.

This Amendment shall be effective as of the Fourth Amendment Effective Date. On and after the Fourth Amendment Effective Date, each reference in the Agreement to "this Agreement," "hereunder," "hereof," "herein" or words of like import, and each similar reference in the other documents entered into in connection with the Agreement, shall mean and be a reference to the Agreement, as amended by this Amendment. Except as specifically amended above, the Agreement shall remain in full force and effect in accordance with its terms and is hereby ratified and confirmed.

This Amendment shall be governed by and construed in accordance with the laws of the State of New York, without reference to its conflict of laws principles, and shall not be governed by the United Nations Convention of International Contracts on the Sale of Goods (the Vienna Convention).

*[Signature page follows.]*

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IN WITNESS WHEREOF, the parties have caused this Amendment to be executed by their duly authorized representatives.

**Blueprint Medicines Corporation**

/s/ Jeffrey W. Albers

Name: Jeffrey W. Albers  
Title: Chief Executive Officer

**F. Hoffmann-La Roche Ltd**

/s/ Stefan Arnold

Name: Stefan Arnold  
Title: Head Legal Pharma

/s/ Barbara Luekel

Name: Barbara Luekel  
Title: Global Business Development Director

**Hoffmann-La Roche Inc.**

/s/ John P. Parise

Name: John P. Parise  
Title: Authorized Signatory

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**Subsidiaries of the Registrant**

<u>Entity</u>	<u>State of Incorporation or Organization</u>
Blueprint Medicines Security Corporation	Massachusetts
Blueprint Medicines (Switzerland) GmbH	Switzerland
Blueprint Medicines (Netherlands) B.V.	Netherlands

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**Consent of Independent Registered Public Accounting Firm**

We consent to the incorporation by reference in the following Registration Statements:

- (1) Registration Statement (Form S-3 No. 333-216573) of Blueprint Medicines Corporation,
- (2) Registration Statement (Form S-8 No. 333-203749) pertaining to the 2011 Stock Option and Grant Plan, 2015 Stock Option and Incentive Plan, and 2015 Employee Stock Purchase Plan of Blueprint Medicines Corporation, and
- (3) Registration Statements (Form S-8 Nos. 333-210125, 333-216575 and 333-223131) pertaining to the 2015 Stock Option and Incentive Plan and 2015 Employee Stock Purchase Plan of Blueprint Medicines Corporation;

of our reports dated February 26, 2019, with respect to the consolidated financial statements of Blueprint Medicines Corporation and the effectiveness of internal control over financial reporting of Blueprint Medicines Corporation included in this Annual Report (Form 10-K) of Blueprint Medicines Corporation for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 26, 2019

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## CERTIFICATIONS

I, Jeffrey W. Albers, certify that:

1. I have reviewed this Annual Report on Form 10-K of Blueprint Medicines Corporation;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
  - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
  - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 26, 2019

By: /s/ Jeffrey W. Albers  
Jeffrey W. Albers  
President and Chief Executive Officer  
(Principal Executive Officer)

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## CERTIFICATIONS

I, Michael Landsittel, certify that:

1. I have reviewed this Annual Report on Form 10-K of Blueprint Medicines Corporation;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
  - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
  - (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 26, 2019

By: /s/ Michael Landsittel

Michael Landsittel  
Chief Financial Officer  
(Principal Financial and Accounting Officer)

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

In connection with the Annual Report on Form 10-K of Blueprint Medicines Corporation (the "Company") for the year ended December 31, 2018 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company hereby certifies, pursuant to 18 U.S.C. Section 1350, that to his knowledge:

- (1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 26, 2019

By: /s/ Jeffrey W. Albers  
Jeffrey W. Albers  
President and Chief Executive Officer  
*(Principal Executive Officer)*

Date: February 26, 2019

By: /s/ Michael Landsittel  
Michael Landsittel  
Chief Financial Officer  
*(Principal Financial and Accounting Officer)*

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