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**Filed Pursuant to Rule 424(b)(5)
Registration No. 333-216573**

Title of Each Class of Securities to be Registered	Amount to be Registered ⁽¹⁾	Proposed Maximum Offering Price Per Unit	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee ⁽²⁾
Common Stock, par value \$0.001 per share	4,662,162	\$ 74.00	\$ 344,999,988	\$ 41,814

⁽¹⁾ Includes 608,108 shares of common stock, par value \$0.001 per share, which may be purchased by the underwriters upon exercise of the underwriters' option to purchase additional shares.

⁽²⁾ Calculated in accordance with Rule 456(b) and 457(r) of the Securities Act of 1933, as amended.

Prospectus Supplement to Prospectus dated March 9, 2017.

4,054,054 Shares



Blueprint Medicines Corporation

Common Stock

We are selling 4,054,054 shares of our common stock.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "BPMC." The last reported sale price of our common stock on the Nasdaq Global Select Market on March 28, 2019 was \$75.71 per share.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page S-13 of this prospectus supplement, as well as in the documents incorporated or deemed to be incorporated by reference into this prospectus supplement and the accompanying prospectus, for a discussion of the factors you should carefully consider before deciding to purchase our common stock.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

	Per share	Total
Public offering price	\$ 74.00	\$ 299,999,996
Underwriting discount ⁽¹⁾	\$ 3.70	\$ 15,000,000
Proceeds, before expenses, to Blueprint Medicines Corporation	\$ 70.30	\$ 284,999,996

⁽¹⁾ We refer you to "Underwriting" beginning on page S-21 of this prospectus supplement for additional information regarding underwriter compensation.

We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to an additional 608,108 shares of our common stock at the public offering price less the underwriting discounts and commissions.

The underwriters expect to deliver the shares against payment in New York, New York on or about April 2, 2019.

**Goldman Sachs & Co. LLC
Guggenheim Securities**

**Cowen
Wedbush PacGrow**

Prospectus Supplement dated March 28, 2019

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PROSPECTUS

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of the registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process and consists of two parts. The first part is this prospectus supplement, including the documents incorporated by reference herein, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference therein, gives more general information, some of which may not apply to this offering. Generally, when we refer to the "prospectus", we are referring to both parts combined. This prospectus supplement may add to, update or change information in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus.

If information in this prospectus supplement is inconsistent with the accompanying prospectus or with any document incorporated by reference herein or therein that was filed with the SEC before the date of this prospectus supplement, you should rely on this prospectus supplement. This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into each include important information about us, the securities being offered and other information you should know before investing in our securities. You should also read and consider information in the documents we have referred you to in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Incorporation by Reference" and the accompanying prospectus entitled "Where You Can Find More Information" and "Incorporation by Reference".

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We take no responsibility for, and can provide no assurances as to the reliability of, any information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We are not offering to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than as of the date of this prospectus supplement or the accompanying prospectus, as the case may be, or in the case of the documents incorporated by reference herein or therein, the date of such documents regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our securities. Our business, financial condition, liquidity, results of operations and prospects may have changed since those dates.

We are not making offers to sell shares of our common stock or soliciting offers to purchase shares of our common stock in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation.

Unless otherwise stated, all references in this prospectus supplement or the accompanying prospectus to "us", "our", "Blueprint", "Blueprint Medicines", "we", the "Company" and similar designations refer, collectively, to Blueprint Medicines Corporation, a Delaware corporation, and its consolidated subsidiaries.

No action is being taken in any jurisdiction outside the United States to permit a public offering of the securities or possession or distribution of this prospectus supplement or the accompanying prospectus in that jurisdiction. Persons who come into possession of this prospectus supplement or the accompanying prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement or the accompanying prospectus applicable to that jurisdiction.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at www.blueprintmedicines.com. Our website is not a part of this prospectus supplement or the accompanying prospectus and is not incorporated by reference in this prospectus supplement or the accompanying prospectus.

This prospectus supplement is part of a registration statement we filed with the SEC. This prospectus supplement, filed as part of the registration statement, omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information on us and our consolidated subsidiaries and the securities we are offering. Statements in this prospectus supplement concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's website.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and those future filings may modify or supersede some of the information included or incorporated by reference in this prospectus supplement. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement, the accompanying prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus supplement incorporates by reference the documents listed below (File No. 001-37359) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of this prospectus supplement and the termination of this offering:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2018, filed with the SEC on February 26, 2019;
- The portions of our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 27, 2018, incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2017;

- Current Reports on Form 8-K filed on February 5, 2019, March 8, 2019 and March 27, 2019; and
- The description of our common stock contained in our Registration Statement on Form 8-A filed on April 27, 2015, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by contacting us, either orally or in writing, at the following:

Blueprint Medicines Corporation
45 Sidney Street
Cambridge, Massachusetts 02139
Attn: Investor Relations
Phone: (617) 714-6674
E-mail: ir@blueprintmedicines.com

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain statements that are not historical facts and are considered forward-looking within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical facts, contained or incorporated by reference in this prospectus 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. Forward-looking statements include, but are not limited to, statements about:

- our use of the net proceeds from this offering;
- 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, including planned new drug applications to the U.S. Food and Drug Administration or marketing authorization applications to the European Medicines Agency;
- 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.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, particularly in the "Risk Factors" section beginning on page S-10 of this prospectus supplement and on page 45 of our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, as filed with the SEC on February 26, 2019, that could cause actual results or events to differ materially from the forward-looking

statements that we make. 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 prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein, as well as the documents that we have filed as exhibits to the registration statement of which this prospectus forms a part, 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 prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein also contain 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.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents incorporated by reference herein or therein. This summary does not contain all the information that you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under "Risk Factors" beginning on page S-13 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. This prospectus supplement may add to, update or change information in the accompanying prospectus.

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.

Clinical Programs

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 expect to complete enrollment of the VOYAGER trial in the second half of 2019. In November 2018, we reported updated data from the NAVIGATOR trial at the Connective Tissue Oncology Society Annual Meeting, and in January 2019, we reported top-line data from the NAVIGATOR trial. We plan to present additional data from the NAVIGATOR trial in the second quarter 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, to the U.S. Food and Drug Administration, or FDA, for avapritinib for the treatment of PDGFRA Exon 18 mutant GIST and fourth-line GIST in the second quarter of 2019, and if approved, we plan to submit a supplemental NDA to the FDA for the treatment of third-line GIST in 2020. Please see "— Recent Developments" below for plans to submit a marketing authorization application to the European Medicines Agency for avapritinib in GIST.

In addition, 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. In December 2018, we reported updated data from the EXPLORER trial at the 60th American Society of Hematology Annual Meeting and Exposition, and 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 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. Please see "— Recent Developments" below for updated plans to submit an NDA to the FDA for avapritinib for the treatment of advanced SM. The 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. In April 2018, we presented initial data from the ongoing ARROW trial at the American Association for Cancer Research, and in October 2018, we presented updated data from the ongoing ARROW trial in RET-altered MTC and PTC at the 88th Annual Meeting of the American Thyroid Association. Please see "— Recent Developments" below for updated top-line data for BLU-667 in RET-fusion NSCLC, plans to present updated RET-fusion NSCLC and RET-mutant MTC data in the second quarter of 2019 and updated plans to submit an NDA to the FDA for BLU-667 for the treatment of RET-fusion NSCLC. 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 19th World Conference on Lung Cancer and published online in *Cancer Discovery*. In the second half of 2019, we plan to initiate a Phase 3 clinical trial evaluating BLU-667 in first-line RET-fusion 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. In October 2018, we presented foundational pre-clinical data for our FOP program at the 2018 American Society for Bone and Mineral Research Annual Meeting, and we initiated a Phase 1 clinical trial in healthy volunteers in the first quarter of 2019. Please see "— Recent Developments" below for updated plans to initiate a Phase 2a clinical trial of BLU-782 in patients with FOP. The FDA has granted fast track designation to BLU-782 for the prevention of heterotopic ossification in patients with FOP.

Preclinical Development Programs

We plan to continue to leverage our discovery platform to systematically and reproducibly identify kinases that are drivers of diseases in genomically defined patient populations and craft drug candidates that potently and selectively target these kinases. 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.

Development and Commercialization Rights

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 collaboration with F. Hoffmann La Roche Ltd and Hoffmann La Roche Inc., which we collectively refer to as Roche.

Collaborations

We entered into collaborations with 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.

Recent Developments

Avapritinib for the Treatment of GIST

We plan to submit a marketing authorization application to the European Medicines Agency for avapritinib for the treatment of PDGFRa D842V mutant GIST and fourth-line GIST in the third quarter of 2019.

Avapritinib for the Treatment of Advanced SM

We now plan to submit an NDA to the FDA for avapritinib for the treatment of advanced SM in the first quarter of 2020, subject to continued discussions with the FDA under its breakthrough therapy program to determine whether the clinical data from the ongoing Phase 1 EXPLORER trial and the initial clinical data from the ongoing Phase 2 PATHFINDER trial will support an NDA submission.

BLU-667 for the Treatment of RET-altered Cancers

In the ongoing Phase 1 ARROW trial, 34 patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy and 16 patients with RET-mutant MTC previously treated with the multi-kinase inhibitors cabozantinib and/or vandetanib were response evaluable at the recommended Phase 2 dose of 400 mg once daily as of November 14, 2018 with follow-up through a data cutoff date of March 1, 2019. In these RET-fusion NSCLC patients, the overall response rate was 62 percent (95 percent confidence interval: 44-78 percent; 21 patients with partial responses, 5 pending confirmation), and in these RET-mutant MTC patients, the overall response rate was 63 percent (95% confidence interval: 35-85 percent; 10 patients with partial responses, 3 pending confirmation). As of the data cutoff date, BLU-667 was generally well-tolerated, and most adverse events, or AEs, reported by investigators were mild to moderate (Grade 1 or Grade 2). Across all doses and treatment cohorts (n=217), only eight patients (3.7 percent) discontinued treatment with BLU-667 due to treatment-related AEs. One patient with metastatic NSCLC passed away (Grade 5) due to pneumonia/lung infection that was determined by the investigator to be possibly related to BLU-667. Detailed safety and clinical data from the ARROW trial in RET-fusion NSCLC patients and RET-mutant MTC patients have been submitted for presentation at the American Society of Clinical Oncology Annual Meeting in June 2019.

In addition, the enrollment target has been reached and patient screening is now closed for the registration-enabling ARROW trial cohort for patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy. We anticipate reaching the enrollment target and closing patient screening for the registration-enabling ARROW trial cohort for patients with RET-mutant MTC previously treated with an approved multi-kinase inhibitor before the end of the second quarter of 2019.

Based on the early achievement of the enrollment target for the RET-fusion NSCLC cohort, we now plan to submit an NDA to the FDA for BLU-667 for the treatment of patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy in the first quarter of 2020. We continue to expect to submit an NDA to the FDA for BLU-667 for the treatment of patients with RET-mutant MTC previously treated with an approved multi-kinase inhibitor in the first half of 2020.

BLU-782 for the Treatment of Fibrodysplasia Ossificans Progressiva

Based on the progress of the ongoing Phase 1 clinical trial of BLU-782 in healthy volunteers and input from clinical experts, we now plan to initiate a Phase 2a clinical trial of BLU-782 in patients with FOP in the fourth quarter of 2019.

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-fusion NSCLC and RET-mutant 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.

Company Information

We were incorporated in Delaware in October 2008. Our mailing address and executive offices are located at 45 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 374-7580. We maintain an Internet website at the following address: www.blueprintmedicines.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus supplement or the accompanying prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock. Our common stock trades on the Nasdaq Global Select Market under the symbol "BPMC".

The trademarks, trade names and services marks appearing in this prospectus supplement and the accompanying prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

THE OFFERING

Common stock offered by us	4,054,054 shares
Common stock outstanding following the offering	48,091,080 shares (or 48,699,188 shares if the underwriters exercise their option to purchase additional shares in full)
Underwriters' option to purchase additional shares	We have granted the underwriters an option to purchase up to an additional 608,108 shares of common stock. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of proceeds	We expect to receive net proceeds from this offering of approximately \$284.5 million (or approximately \$327.2 million if the underwriters exercise their option to purchase additional shares in full), after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to further build our commercial infrastructure and operations in support of one or more anticipated commercial launches of our drug candidates; to fund clinical trials for avapritinib in GIST and SM; to fund clinical trials for BLU-667 in RET-driven cancers; to fund a planned Phase 2a clinical trial for BLU-782 in patients with FOP; to fund manufacturing costs for ongoing and anticipated drug development efforts for our most advanced drug candidates; and the balance, if any, to fund additional research, other clinical trials, working capital requirements and other general corporate purposes. See "Use of Proceeds" for additional information.
Risk factors	Investing in our common stock involves risks. See "Risk Factors" beginning on page S-13 of this prospectus supplement and other information included or incorporated by reference into this prospectus supplement and the accompanying prospectus for a discussion of the factors you should carefully consider before deciding to invest in our securities.
Nasdaq Global Select Market symbol	"BPMC"

The number of shares of our common stock to be outstanding after the offering is based on 44,037,026 shares of common stock outstanding as of December 31, 2018 and excludes:

- 4,557,800 shares of common stock issuable upon the exercise of stock options outstanding as of December 31, 2018, at a weighted average exercise price of \$44.64 per share;
- 36,868 shares of common stock issuable upon the vesting and settlement of restricted stock units outstanding as of December 31, 2018;
- 1,776,005 shares of common stock reserved for future issuance under our 2015 Stock Option and Incentive Plan, or the 2015 Plan, as of December 31, 2018, plus any future

increases in the number of shares of common stock reserved for issuance under the 2015 Plan pursuant to the evergreen provision of the 2015 Plan; and

- 1,228,430 shares of common stock reserved for future issuance under our 2015 Employee Stock Purchase Plan as of December 31, 2018.

Except as otherwise indicated, all information in this prospectus supplement assumes:

- no exercise by the underwriters of their option to purchase up to an additional 608,108 shares of common stock in this offering;
- no exercise of stock options after December 31, 2018; and
- no vesting of restricted stock units after December 31, 2018.

RISK FACTORS

Investing in our common stock involves significant risks. In addition to the other information contained in this prospectus supplement, the accompanying prospectus and in the documents that we have incorporated by reference, you should carefully consider the risks discussed below and under the heading "Risk Factors" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, filed with the SEC on February 26, 2019, as updated by our subsequent filings under the Exchange Act, before making a decision about investing in our common stock. Such risks and uncertainties and those discussed below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business. If any of these risks occur, our business, financial condition and operating results could be harmed, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks Related to Our Common Stock and this Offering

The price of our common stock historically has been and may in the future be volatile and fluctuate substantially, which may affect the price at which you could sell the common stock.

Our stock price has been, and in the future may 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 March 28, 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.

We have broad discretion in how we use the proceeds of this offering, as well as our existing cash, cash equivalents and investments, and may not use them effectively, which could affect our results of operations and cause our stock price to decline.

We will have considerable discretion in the application of the net proceeds of this offering, including for any of the purposes described in the section entitled "Use of Proceeds," as well as our existing cash, cash equivalents and investments, and you will be relying on the judgment of our management regarding such application. You will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. As a result, investors will be relying upon management's judgment with only limited information about our specific intentions for the use of the balance of the net proceeds of this offering. We may use the net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

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.

The holdings of our executive officers, directors and stockholders who own more than 5% of our outstanding common stock, together with their affiliates and related persons, represent beneficial ownership, in the aggregate, of approximately 47% of our common stock, based on the number of shares of our common stock outstanding as of December 31, 2018. Upon the closing of this offering, the holdings of our executive officers, directors and stockholders who owned more than 5% of our outstanding common stock before this offering, together with their affiliates and related persons, will represent beneficial ownership, in the aggregate, of approximately 43.1% of our common stock (or approximately 42.6% if the underwriters exercise in full their option to purchase additional shares), based on the number of shares of our common stock outstanding as of December 31, 2018. 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 acquirer from making a tender offer or otherwise attempting to obtain control of us.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing shares of common stock in this offering will pay a price per share that substantially exceeds the as adjusted book value per share of our tangible assets as of December 31, 2018 after subtracting our liabilities. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of \$59.37 per share, based on the difference between the public offering price of \$74.00 per share and the as adjusted net tangible book value per share of our outstanding common stock as of December 31, 2018.

This dilution is due to the substantially lower price paid by some of our investors who purchased shares prior to this offering as compared to the price offered to the public in this offering, and the exercise of stock options granted to our employees. In addition, as of December 31, 2018, options to purchase 4,557,800 shares of our common stock at a weighted average exercise price of \$44.64 per share were outstanding, and 36,868 restricted stock units were outstanding. Each restricted stock unit represents a contingent right to receive one share of our common stock. The exercise of any of these options and the vesting and settlement of any of these restricted stock units would result in additional dilution. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of our liquidation. Further, because we will need to raise additional capital to fund our future activities, we may in the future sell substantial amounts of common stock or securities convertible into or exchangeable for common stock.

These future issuances of common stock or common stock-related securities, together with the vesting and exercise of outstanding options, the vesting and settlement of outstanding restricted stock units and any additional shares issued in connection with acquisitions, if any, may result in further dilution. For a further description of the dilution that you will experience immediately after this offering, see "Dilution."

Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

In addition, the sale of substantial amounts of our common stock could adversely impact its price. As of December 31, 2018, 44,037,026 shares of our common stock were outstanding, excluding options to purchase 4,557,800 shares of our common stock, of which 2,103,540 were exercisable as of that date, and 36,868 shares of unvested restricted stock units. The sale or the availability for sale of a large number of shares of our common stock in the public market could cause the price of our common stock to decline.

We and our directors and executive officers have agreed that for a period of 75 days after the date of this prospectus supplement, in each case, subject to specified exceptions, we or they will not offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock. These lock-up periods affect approximately 446,592 shares of our common stock outstanding as of December 31, 2018. In addition, the representatives of the underwriters may, in their sole discretion, release all or some portion of the shares subject to such lock-up restrictions at any time and for any reason. Sales of

stock by any of our directors, executive officers or principal stockholders could have a material adverse effect on the trading price of our common stock.

Certain holders of shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. See "Description of Capital Stock — Registration Rights" in the accompanying prospectus. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares purchased by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

USE OF PROCEEDS

We expect to receive net proceeds of approximately \$284.5 million from this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, or approximately \$327.2 million if the underwriters exercise in full their option to purchase up to an additional 608,108 shares of common stock.

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

We intend to use the net proceeds from this offering, plus, if needed, existing cash, cash equivalents and investments, as follows:

- to further build our commercial infrastructure and operations in support of one or more anticipated commercial launches of our drug candidates, including potential commercial launches of avapritinib in the United States and Europe, subject to regulatory approval;
- to fund clinical trials for avapritinib in GIST and SM, including our planned registration-enabling Phase 3 COMPASS-2L clinical trial for second-line GIST and our ongoing registration-enabling Phase 2 PIONEER clinical trial for indolent and smoldering SM, as well as future indication expansion clinical trials;
- to fund clinical trials for BLU-667 in RET-driven cancers, including our planned Phase 3 clinical trial for BLU-667 in first-line RET-altered NSCLC and our planned Phase 2 clinical trial for BLU-667 in combination with osimertinib in treatment-resistant, EGFR-mutant NSCLC harboring an acquired RET alteration;
- to fund a planned Phase 2a clinical trial for BLU-782 in patients with FOP;
- to fund manufacturing costs for ongoing and anticipated drug development efforts for our most advanced drug candidates, including a potential commercial launch of avapritinib; and
- the balance, if any, to fund additional discovery research efforts, our other ongoing and planned clinical trials, working capital requirements and other general corporate purposes.

Based on our current plans, we believe our cash, cash equivalents and investments, together with the net proceeds to us from this offering, but 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 middle of 2021.

This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. As of the date of this prospectus supplement, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering, the amounts that we will actually spend on the uses set forth above or the timing of such expenditures. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from non-clinical studies and ongoing clinical trials or any clinical trials we may commence in the future, the scope and results of our regulatory activities, and the nature and scope of our commercial launch preparation activities, as well as any collaborations that we may enter into with third parties for our drug candidates and any unforeseen cash needs. In addition, we believe opportunities may exist from time to time to expand our current business through acquisitions or in-licenses of complementary companies, medicines or technologies. While we have no current agreements, commitments or understandings for any specific acquisitions or in-licenses at this time, we may use a portion of the net proceeds for these purposes. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted to the extent of the difference between the price per share of our common stock in this offering and the as adjusted net tangible book value per share of our common stock immediately after this offering.

As of December 31, 2018, we had net tangible book value of approximately \$419.0 million, or \$9.51 per share of our common stock, based upon 44,037,026 shares of our common stock outstanding as of that date. Historical net tangible book value per share is equal to our total tangible assets, less total liabilities, divided by the number of outstanding shares of our common stock. Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the sale of 4,054,054 shares of common stock in this offering at the public offering price of \$74.00 per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of December 31, 2018 would have been approximately \$703.5 million, or approximately \$14.63 per share of common stock. This represents an immediate increase in as adjusted net tangible book value of \$5.12 per share to our existing stockholders and an immediate dilution of \$59.37 per share to investors participating in this offering at the public offering price of \$74.00 per share.

Dilution per share to new investors is determined by subtracting net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this per share dilution (assuming the underwriters do not exercise in full their option to purchase additional shares):

Public offering price per share	\$ 74.00
Historical net tangible book value per share as of December 31, 2018	\$ 9.51
Increase in net tangible book value per share attributable to new investors	\$ 5.12
As adjusted net tangible book value per share after this offering	\$ 14.63
Dilution per share to new investors	\$ 59.37

The foregoing table and discussion is based on 44,037,026 shares of common stock outstanding as of December 31, 2018, and excludes:

- 4,557,800 shares of common stock issuable upon the exercise of stock options outstanding as of December 31, 2018, at a weighted average exercise price of \$44.64 per share;
- 36,868 shares of common stock issuable upon the vesting and settlement of restricted stock units outstanding as of December 31, 2018;
- 1,776,005 shares of common stock reserved for future issuance under the 2015 Plan as of December 31, 2018; and
- 1,228,430 shares of common stock reserved for future issuance under our 2015 Employee Stock Purchase Plan as of December 31, 2018.

If the underwriters exercise in full their option to purchase up to an additional 608,108 shares of our common stock at the public offering price of \$74.00 per share, the as adjusted net tangible book value after this offering would be \$15.32 per share, representing an increase in net tangible book value of \$5.81 per share to existing stockholders and immediate dilution in net tangible book value of \$58.68 per share to investors purchasing our common stock in this offering at the assumed public offering price of \$74.00.

To the extent that any options are vested and exercised or any restricted stock units are vested and settled, new options or restricted stock units are issued under our equity incentive plans, or we otherwise issue additional shares of common stock in the future (including shares issued in connection with acquisitions), there will be further dilution to new investors.

In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

DIVIDEND POLICY

We have never declared or paid dividends on our capital stock. We do not anticipate paying any dividends on our capital stock in the foreseeable future. We currently intend to retain all available funds and any future earnings to fund the development and growth of our business. Any future determination to declare dividends will be subject to 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 dividends.

UNDERWRITING

We have entered into an underwriting agreement with the underwriters named below with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. Goldman Sachs & Co. LLC and Cowen and Company, LLC are acting as representatives of the underwriters.

Underwriters	Number of Shares
Goldman Sachs & Co. LLC	2,148,649
Cowen and Company, LLC	1,418,919
Guggenheim Securities, LLC.	243,243
Wedbush Securities Inc.	243,243
Total	4,054,054

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

The underwriters have an option to buy up to 608,108 additional shares of our common stock from us. They may exercise this option for 30 days. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by us. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to 608,108 additional shares of our common stock.

Paid by the Company

	No Exercise	Full Exercise
Per Share	\$ 3.70	\$ 3.70
Total	\$ 15,000,000	\$ 17,249,999

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to \$2.22 per share from the public offering price. After the offering of the shares, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We and our directors and executive officers have agreed that for a period of 75 days after the date of this prospectus supplement, in each case, subject to specified exceptions, that neither we nor they will offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock, except with the prior written consent of the representatives. These lock-up periods affect approximately 446,592 shares of our common stock outstanding as of December 31, 2018. The lock-up restrictions are subject to certain exceptions, including transfers of shares of our common stock (i) acquired in the open market following the completion of this offering; (ii) as a bona fide gift, to a trust for the benefit of the holder or his or her immediate family, by will or other testamentary document or intestate succession, or by operation of law; (iii) to an affiliate of the holder or as part of a distribution

without consideration to a holder's stockholders, partners, members or other equity holders; (iv) in connection with an exercise for cash of options to purchase our common stock, the "net exercise" or "cashless" exercise of such options within 90 days of the expiration of such options, and any transfer for the payment of taxes due as result of the exercise of such options or the vesting and settlement of restricted stock units; and (v) in connection with establishing a trading plan pursuant to Rule 10b5-1, or 10b5-1 plan, under the Securities Exchange Act of 1934, as amended. The representatives, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

Our common stock is publicly traded on the Nasdaq Global Select Market under the symbol "BPMC".

In connection with this offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by subsequent purchases. A "covered short position" is a short position that is not greater than the amount of additional shares for which the underwriters' option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to cover the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option described above. "Naked" short sales are any short sales that create a short position greater than the amount of additional shares for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of our common stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on the Nasdaq Global Select Market, in the over-the-counter market or otherwise.

The underwriters do not expect sales to discretionary accounts to exceed five percent of the total number of shares offered.

We estimate that our share of the total expenses of the offering, excluding underwriting discounts and commissions, will be approximately \$500,000. This includes reimbursement to the underwriters for certain of their expenses in an amount up to \$25,000.

We have agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933, as amended.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to us and to persons and entities with relationships with us, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively traded securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to our assets, securities and/or instruments (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with us. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of our common shares may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of our common shares may be made at any time under the following exemptions under the Prospectus Directive:

- To any legal entity which is a qualified investor as defined in the Prospectus Directive;
- To fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), subject to obtaining the prior consent of the representatives for any such offer; or
- In any other circumstances falling within Article 3(2) of the Prospectus Directive;

provided that no such offer or shares of our common stock shall result in a requirement for the publication by us or any Brazilian placement agent of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to public" in relation to our common shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and our common shares to be offered so as to enable an investor to decide to purchase our common shares, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (as amended), including by Directive 2010/73/EU and includes any relevant implementing measure in the Relevant Member State.

This European Economic Area selling restriction is in addition to any other selling restrictions set out below.

United Kingdom

In the United Kingdom, this prospectus is only addressed to and directed as qualified investors who are (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order); or (ii) high net worth entities and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons"). Any investment or investment activity to which this prospectus relates is available only to relevant persons and will only be engaged with relevant persons. Any person who is not a relevant person should not act or rely on this prospectus or any of its contents.

France

Neither this prospectus nor any other offering material relating to the shares described in this prospectus has been submitted to the clearance procedures of the Autorité des Marchés Financiers or of the competent authority of another member state of the European Economic Area and notified to the Autorité des Marchés Financiers. The shares have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus nor any other offering material relating to the shares has been or will be:

- released, issued, distributed or caused to be released, issued or distributed to the public in France; or
- used in connection with any offer for subscription or sale of the shares to the public in France.

Such offers, sales and distributions will be made in France only:

- to qualified investors (investisseurs qualifiés) and/or to a restricted circle of investors (cercle restreint d'investisseurs), in each case investing for their own account, all as defined in, and in accordance with articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French Code monétaire et financier;
- to investment services providers authorized to engage in portfolio management on behalf of third parties; or
- in a transaction that, in accordance with article L.411-2-II-1°-or-2°-or 3° of the French Code monétaire et financier and article 211-2 of the General Regulations (Règlement Général) of the Autorité des Marchés Financiers, does not constitute a public offer (appel public à l'épargne).

The shares may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French Code monétaire et financier.

Australia

No prospectus or other disclosure document (as defined in the Corporations Act 2001 (Cth) of Australia ("Corporations Act")) in relation to the common stock has been or will be lodged with the Australian Securities & Investments Commission ("ASIC"). This document has not been lodged with ASIC and is only directed to certain categories of exempt persons. Accordingly, if you receive this document in Australia:

- you confirm and warrant that you are either:
 - a "sophisticated investor" under section 708(8)(a) or (b) of the Corporations Act;

- a "sophisticated investor" under section 708(8)(c) or (d) of the Corporations Act and that you have provided an accountant's certificate to us which complies with the requirements of section 708(8)(c)(i) or (ii) of the Corporations Act and related regulations before the offer has been made;
 - a person associated with the company under section 708(12) of the Corporations Act; or
 - a "professional investor" within the meaning of section 708(11)(a) or (b) of the Corporations Act, and to the extent that you are unable to confirm or warrant that you are an exempt sophisticated investor, associated person or professional investor under the Corporations Act any offer made to you under this document is void and incapable of acceptance; and
- you warrant and agree that you will not offer any of the common stock for resale in Australia within 12 months of that common stock being issued unless any such resale offer is exempt from the requirement to issue a disclosure document under section 708 of the Corporations Act.

Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32 of the Laws of Hong Kong) ("Companies (Winding Up and Miscellaneous Provisions) Ordinance") or which do not constitute an invitation to the public within the meaning of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) ("Securities and Futures Ordinance"), or (ii) to "professional investors" as defined in the Securities and Futures Ordinance and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance, and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" in Hong Kong as defined in the Securities and Futures Ordinance and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA")) under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a corporation (which is not an accredited investor (as defined in Section 4A of the

SFA) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for 6 months after that corporation has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore ("Regulation 32")

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a trust (where the trustee is not an accredited investor (as defined in Section 4A of the SFA)) whose sole purpose is to hold investments and each beneficiary of the trust is an accredited investor, the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferable for 6 months after that trust has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer that is made on terms that such rights or interest are acquired at a consideration of not less than S\$200,000 (or its equivalent in a foreign currency) for each transaction (whether such amount is to be paid for in cash or by exchange of securities or other assets), (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The securities may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

Israel

In the State of Israel this prospectus shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728-1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728-1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728-1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728-1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in the First Addendum to the Israeli Securities Law, 5728-1968. In particular, we may request, as a

condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728-1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728-1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728-1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728-1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

Canada

The securities may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions, and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following is a summary of the material U.S. federal income tax consequences of the ownership and disposition of our common stock to non-U.S. holders, but does not purport to be a complete analysis of all the potential tax considerations relating thereto. This summary is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, Treasury regulations promulgated thereunder, administrative rulings and judicial decisions, all as of the date hereof. These authorities may be changed or subject to differing interpretations, possibly with retroactive effect, so as to result in U.S. federal income tax consequences different from those set forth below. We have not sought any ruling from the Internal Revenue Service, or the IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions.

This summary also does not address the tax considerations arising under the laws of any U.S. state or local or any non-U.S. jurisdiction, U.S. federal estate or gift tax laws, the Medicare tax on net investment income or any alternative minimum tax consequences. In addition, this discussion does not address tax considerations applicable to an investor's particular circumstances or to investors that may be subject to special tax rules, including, without limitation:

- banks, insurance companies or other financial institutions;
- tax-exempt organizations;
- dealers in securities or currencies;
- traders in securities that elect to use a mark-to-market method of accounting for their securities holdings;
- persons that own, or are deemed to own, more than five percent of our capital stock;
- certain former citizens or long-term residents of the United States;
- persons who hold our common stock as a position in a hedging transaction, "straddle", "conversion transaction" or other risk reduction transaction;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes);
- S corporations, partnerships, or other entities or arrangements treated as partnerships for U.S. federal income tax purposes (or investors in any such entities);
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- regulated investment companies or real estate investment trusts;
- pension plans;
- qualified foreign pension funds or entities wholly owned by qualified foreign pension funds;
- controlled foreign corporations;
- persons subject to special tax accounting rules as a result of any item of gross income with respect to our common stock being taken into account in an applicable financial statement;
- passive foreign investment companies; or
- persons that acquire our common stock as compensation for services.

In addition, if a partnership, including any entity or arrangement classified as a partnership for U.S. federal income tax purposes, holds our common stock, the tax treatment of a partner in such

partnership generally will depend on the status of the partner and upon the activities of the partnership. Accordingly, partnerships that hold our common stock, and partners in such partnerships, should consult their tax advisors.

You are urged to consult your tax advisor with respect to the application of the U.S. federal income tax laws to your particular situation, as well as any tax consequences of the purchase, ownership and disposition of our common stock arising under the U.S. federal estate or gift tax rules or under the laws of any U.S. state or local or any non-U.S. or other taxing jurisdiction or under any applicable tax treaty.

Non-U.S. Holder Defined

For purposes of this discussion, you are a non-U.S. holder if you are a beneficial owner of our common stock that is for United States federal income tax purposes (i) a foreign corporation, (ii) a nonresident alien individual, (iii) a foreign estate, the income of which, if from sources without the United States and not effectively connected with the conduct of a trade or business within the United States, is not subject to tax in the United States; or (iv) a trust that has not made an election to be treated as a U.S. holder under applicable Treasury regulations and that either (A) is not subject to the primary jurisdiction of a court within the United States, or (B) is not subject to the substantial control of one or more United States persons.

Distributions

As discussed under "Dividend Policy", above, we do not anticipate paying any dividends on our capital stock in the foreseeable future. If we were to make distributions on our common stock, those payments will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed both our current and our accumulated earnings and profits, they will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock, subject to the tax treatment described in the discussion below regarding taxable dispositions of our common stock. Any such distributions would also be subject to the discussions below regarding backup withholding and FATCA.

Subject to the discussion below regarding a dividend received by you that is effectively connected with the conduct of a U.S. trade or business, a dividend paid to you generally will be subject to U.S. withholding tax either at a rate of 30% of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty. In order to receive a reduced treaty rate, you must provide us with a valid IRS Form W-8BEN, IRS Form W-8-BEN-E or another appropriate version of IRS Form W-8 (or a successor form), in each case, certifying qualification for the reduced rate.

Dividends received by you that are effectively connected with the conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, are attributable to a permanent establishment maintained by you in the United States) generally are exempt from such withholding tax. In order to obtain this exemption, you must provide us with a valid IRS Form W-8ECI or successor form or other applicable IRS Form W-8 properly certifying such exemption. Such effectively connected dividends, although not subject to withholding tax, are taxed at the same graduated rates applicable to U.S. persons, net of certain deductions and credits, subject to an applicable income tax treaty providing otherwise. In addition, if you are a corporate non-U.S. holder, you may also be subject to a branch profits tax at a rate of 30% or such lower rate as may be specified by an applicable income tax treaty on your earnings and profits in respect of such effectively connected dividend income.

If you are eligible for a reduced rate of withholding tax pursuant to a tax treaty, you may be able to obtain a refund of any excess amounts currently withheld if you file an appropriate claim for refund with the IRS.

Gain on Sale or Other Taxable Disposition of Common Stock

Subject to the discussion below regarding backup withholding, a non-U.S. Holder generally will not be required to pay U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, the gain is attributable to a permanent establishment maintained by you in the U.S.), in which case you will be required to pay tax on the net gain derived from the sale under regular graduated U.S. federal income tax rates, and for a non-U.S. holder that is a corporation, such non-U.S. holder may be subject to the branch profits tax on any earnings and profits attributable to such gains at a 30% rate or such lower rate as may be specified by an applicable income tax treaty;
- you are an individual who is present in the United States for a period or periods aggregating 183 days or more during the taxable year in which the sale or disposition occurs and certain other conditions are met, in which case you will be required to pay a flat 30% tax on the gain derived from the sale, which tax may be offset by certain U.S. source capital losses in the taxable year of disposition (even though you are not considered a resident of the United States) (subject to applicable income tax or other treaties); or
- our common stock constitutes a U.S. real property interest by reason of our status as a "U.S. real property holding corporation" for U.S. federal income tax purposes, or a USRPHC, at any time within the shorter of the five-year period preceding the disposition or your holding period for our common stock. We believe that we are not currently and will not become a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property relative to the fair market value of our other real property and business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is regularly traded on an established securities market (as determined under the Code), such common stock will be treated as U.S. real property interests only if you actually or constructively hold more than five percent of such regularly traded common stock at any time during the applicable period that is specified in the Code.

Backup Withholding and Information Reporting

Generally, we must report annually to the IRS the amount of dividends paid to you, your name and address, and the amount of tax withheld, if any. A similar report will generally be sent to you. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in your country of residence.

Payments of dividends or of proceeds on the disposition of stock made to you may be subject to additional information reporting and backup withholding at the then applicable rate unless you establish an exemption, for example by properly certifying your non-U.S. status on an IRS Form W-8BEN, IRS Form W-8BEN-E or another appropriate version of IRS Form W-8 (or a successor form). Notwithstanding the foregoing, backup withholding and information reporting may apply if either we or our paying agent has actual knowledge, or reason to know, that you are a U.S. person.

Backup withholding is not an additional tax; rather, the U.S. income tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund or credit may generally be obtained from the IRS, provided that the required information is furnished to the IRS in a timely manner.

Foreign Account Tax Compliance Act ("FATCA")

Provisions commonly referred to as "FATCA" may impose withholding tax on certain types of payments made to "foreign financial institutions" and certain other non-U.S. entities. The legislation imposes a 30% withholding tax on dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution or to certain non-financial foreign entities, unless (i) the foreign financial institution undertakes certain diligence and reporting obligations, (ii) the non-financial foreign entity either certifies it does not have any substantial U.S. owners or furnishes identifying information regarding each substantial U.S. owner and such entity meets certain other specified requirements, or (iii) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the requirements in (i) above, it must enter into an agreement with the U.S. Treasury requiring, among other things, that it undertake to identify accounts held by certain U.S. persons or U.S.-owned foreign entities, annually report certain information about such accounts, and withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. If the country in which a payee is resident has entered into an "intergovernmental agreement" with the United States regarding FATCA, that agreement may permit the payee to report to that country rather than to the U.S. Treasury. Notwithstanding the foregoing, under current proposed Treasury regulations (which taxpayers may rely upon prior to finalization) no withholding will be imposed on gross proceeds from the sale or disposition of our common stock. However, no assurance can be provided that such proposed regulations will not be repealed, or that the final regulations (if and when promulgated) will treat gross proceeds consistently with the proposed regulations. Prospective investors should consult their tax advisors regarding FATCA.

The preceding discussion of U.S. federal income tax considerations is for general information only. It is not tax advice. Each prospective investor should consult its tax advisor regarding the particular U.S. federal, state and local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed change in applicable laws.

LEGAL MATTERS

Certain legal matters with respect to the securities offered by this prospectus supplement will be passed upon for us by Goodwin Procter LLP, Boston, Massachusetts. Certain legal matters will be passed upon for the underwriters by Latham & Watkins LLP.

EXPERTS

The consolidated financial statements of Blueprint Medicines Corporation appearing in Blueprint Medicines Corporation's Annual Report (Form 10-K) for the year ended December 31, 2018 and the effectiveness of Blueprint Medicines Corporation's internal control over financial reporting as of December 31, 2018 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such reports given on the authority of said firm as experts in auditing and accounting.

Blueprint Medicines Corporation

Common Stock
Preferred Stock
Debt Securities
Depository Shares
Purchase Contracts
Purchase Units
Warrants

We may offer and sell securities from time to time in one or more offerings. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement or amendment carefully before you invest in our securities.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Select Market under the symbol "BPMC."

Investing in these securities involves significant risks. See "Risk Factors" included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is March 9, 2017

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ABOUT THIS PROSPECTUS

This prospectus is part of an automatic registration statement that we filed with the Securities and Exchange Commission, which we refer to as the SEC, utilizing a "shelf" registration process as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading "Where You Can Find More Information" beginning on page 3 of this prospectus.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and any accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in any accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless otherwise stated, all references in this prospectus to "us," "our," "Blueprint," "Blueprint Medicines," "we," the "Company" and similar designations refer, collectively, to Blueprint Medicines Corporation, a Delaware corporation, and its consolidated subsidiary, Blueprint Medicines Security Corporation.

RISK FACTORS

Investing in our securities involves significant risks. You should carefully consider the risks and uncertainties described in this prospectus and any accompanying prospectus supplement, including the risk factors set forth in our filings with the SEC that are incorporated by reference herein, including the risk factors in our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and any of our subsequent filings with the SEC, before making an investment decision pursuant to this prospectus and any accompanying prospectus supplement relating to a specific offering.

Our business, financial condition and results of operations could be materially and adversely affected by any or all of these risks or by additional risks and uncertainties not presently known to us or that we currently deem immaterial that may adversely affect us in the future.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at www.blueprintmedicines.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus. You may also read and copy any document we file at the SEC's Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information on us and our consolidated subsidiary and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's website.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 001-37359) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2016;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2015 from our definitive proxy statement (other than information furnished rather than filed) for the 2016 Annual Meeting of Stockholders, which was filed with the SEC on April 28, 2016; and
- The description of our common stock contained in our Registration Statement on Form 8-A filed on April 27, 2015, including any amendments or reports filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by contacting us, either orally or in writing, at the following:

Blueprint Medicines Corporation
38 Sidney Street, Suite 200
Cambridge, Massachusetts 02139
Attn: Investor Relations
Phone: (617) 714-6674
E-mail: ir@blueprintmedicines.com

FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated by reference in this prospectus include "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical facts, contained or incorporated by reference in this prospectus 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. Forward-looking statements include, but are not limited to, statements about the initiation, timing, progress and results of our pre-clinical studies and clinical trials, including our Phase 1 clinical trials for BLU-285, BLU-554 and BLU-667, 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 rare genetic disease collaboration with Alexion Pharma Holding and our existing cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., as well as our ability to enter into other strategic arrangements; the development of companion diagnostic tests for our drug candidates, including our companion diagnostic test with Ventana Medical Systems, Inc. for BLU-554 and our companion diagnostic test with QIAGEN Manchester Limited for BLU-285; our ability to maintain and establish collaborations; our financial performance; and developments relating to our competitors and our industry.

Any forward-looking statements contained or incorporated by reference in this prospectus 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. See "Risk Factors" for more information. 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. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, whether as a result of new information, future events or otherwise.

BLUEPRINT MEDICINES CORPORATION

We are a biopharmaceutical company focused on improving the lives of patients with genomically defined diseases driven by abnormal kinase activation. Our approach is to systematically and reproducibly identify kinases that are drivers of diseases in genomically defined patient populations and to craft drug candidates with therapeutic windows 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 drug novel kinase targets that have been difficult to selectively inhibit. By focusing on diseases in genomically defined patient populations, we believe that we will have a more efficient development path with a greater likelihood of success. Leveraging our novel target discovery engine, we have developed a robust small molecule drug pipeline in cancer and a rare genetic disease.

Our principal executive offices are located at 38 Sidney Street, Suite 200, Cambridge, Massachusetts 02139, and our telephone number is (617) 714-6674.

CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES

The following table sets forth our ratio of earnings to fixed charges for each of the periods indicated. You should read this table in conjunction with the consolidated financial statements and notes incorporated by reference in this prospectus.

	<u>Year Ended December 31,</u>			
	<u>2016</u>	<u>2015</u>	<u>2014</u>	<u>2013</u>
Consolidated ratios of earnings to fixed charges	N/A	N/A	N/A	N/A

For purposes of calculating the consolidated ratios of earnings to fixed charges, earnings consist of net income (loss) plus fixed charges. Fixed charges include interest expense, non-cash interest expense and the interest portion of rent expense which is deemed to be representative of the interest factor.

Our earnings were insufficient to cover fixed charges by \$72.5 million for the year ended December 31, 2016, \$52.8 million for the year ended December 31, 2015, \$40.3 million for the year ended December 31, 2014 and \$20.9 million for the year ended December 31, 2013.

Our ratios of earnings to combined fixed charges and preferred stock dividends for the periods indicated above are the same as our ratios of earnings to fixed charges set forth above.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless the applicable prospectus supplement provides otherwise. General corporate purposes may include research and development costs, the acquisition or licensing of other drugs or drug candidates, business or technologies, repayment and refinancing of debt, working capital and capital expenditures. We may temporarily invest the net proceeds in a variety of capital preservation instruments, including short-term, investment grade, interest bearing instruments and U.S. government securities, until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

DILUTION

If there is a material dilution of the purchasers' equity interest from the sale of common equity securities offered under this prospectus, we will set forth in any prospectus supplement the following information regarding any such material dilution of the equity interests of purchasers purchasing securities in an offering under this prospectus:

- the net tangible book value per share of our equity securities before and after the offering;
- the amount of the increase in such net tangible book value per share attributable to the cash payments made by the purchasers in the offering; and
- the amount of the immediate dilution from the public offering price which will be absorbed by such purchasers.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is intended as a summary only. This description is based upon, and is qualified by reference to, our amended and restated certificate of incorporation, or certificate of incorporation, our amended and restated bylaws, or bylaws, and applicable provisions of the Delaware General Corporation Law. This summary is not complete. You should read our certificate of incorporation and bylaws, which are filed as exhibits to the registration statement of which this prospectus forms a part, for the provisions that are important to you.

Our authorized capital stock consists of 120,000,000 shares of common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, par value \$0.001 per share, all of which are undesignated. As of February 28, 2017, 33,203,902 shares of common stock were outstanding, and no shares of preferred stock were outstanding.

Common Stock

Annual Meeting. Annual meetings of our stockholders are held on the date designated in accordance with our bylaws. Written notice must be mailed to each stockholder entitled to vote not less than ten nor more than 60 days before the date of the meeting. The presence in person or by proxy of the holders of record of a majority of our issued and outstanding shares entitled to vote at such meeting constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of the stockholders may be called for any purpose by the board of directors and shall be called by the chairman of the board or the secretary upon the written request, stating the purpose of such meeting, of the holders of a majority of the outstanding shares of all classes of capital stock entitled to vote at the meeting. Except as may be otherwise provided by applicable law, our certificate of incorporation or our bylaws, all elections shall be decided by a plurality, and all other questions shall be decided by a majority, of the votes cast by stockholders entitled to vote thereon at a duly held meeting of stockholders at which a quorum is present.

Voting Rights. Each holder of common stock is entitled to one vote for each share held on all matters to be voted upon by stockholders.

Dividends. The holders of common stock, after any preferences of holders of any preferred stock, are entitled to receive dividends when and if declared by the board of directors out of legally available funds.

Liquidation and Dissolution. If we are liquidated or dissolved, the holders of the common stock will be entitled to share in our assets available for distribution to stockholders in proportion to the amount of common stock they own. The amount available for common stockholders is calculated after payment of liabilities. Holders of any preferred stock will receive a preferential share of our assets before the holders of the common stock receive any assets.

Other Rights. Holders of the common stock have no right to convert the stock into any other security, have the stock redeemed or purchase additional stock or to maintain their proportionate ownership interest. The common stock does not have cumulative voting rights. Holders of shares of the common stock are not required to make additional capital contributions.

NASDAQ Global Select Market. Our common stock is listed on The NASDAQ Global Select Market under the trading symbol "BPMC."

Transfer Agent and Registrar. Computershare Trust Company, N.A. is the transfer agent and registrar for our common stock.

Preferred Stock

We are authorized to issue "blank check" preferred stock, which may be issued in one or more series upon authorization of our board of directors. Our board of directors is authorized to fix the designation of the series, the number of authorized shares of the series, dividend rights and terms, conversion rights, voting rights, redemption rights and terms, liquidation preferences and any other rights, powers, preferences and limitations applicable to each series of preferred stock. The authorized shares of our preferred stock are available for issuance without further action by our stockholders, unless such action is required by applicable law or the rules of any stock exchange on which our securities may be listed. If the approval of our stockholders is not required for the issuance of shares of our preferred stock, our board may determine not to seek stockholder approval. The specific terms of any series of preferred stock offered pursuant to this prospectus will be described in the prospectus supplement relating to that series of preferred stock.

A series of our preferred stock could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt. Our board of directors will make any determination to issue shares of preferred stock based upon its judgment as to the best interests of our stockholders. Our board of directors, in so acting, could issue preferred stock having terms that could discourage an acquisition attempt through which an acquirer may be able to change the composition of our board of directors, including a tender offer or other transaction that some, or a majority, of our stockholders might believe to be in their best interests or in which stockholders might receive a premium for their stock over the then-current market price of the stock.

The preferred stock has the terms described below unless otherwise provided in the prospectus supplement relating to a particular series of preferred stock. You should read the prospectus supplement relating to the particular series of preferred stock being offered for specific terms, including:

- the designation and stated value per share of the preferred stock and the number of shares offered;
- the amount of liquidation preference per share;
- the price at which the preferred stock will be issued;
- the dividend rate, or method of calculation of dividends, the dates on which dividends will be payable, whether dividends will be cumulative or noncumulative and, if cumulative, the dates from which dividends will commence to accumulate;
- any redemption or sinking fund provisions;
- if other than the currency of the United States, the currency or currencies including composite currencies in which the preferred stock is denominated and/or in which payments will or may be payable;
- any conversion provisions;
- whether we have elected to offer depositary shares as described under "Description of Depositary Shares;" and
- any other rights, preferences, privileges, limitations and restrictions on the preferred stock.

The preferred stock will, when issued, be fully paid and nonassessable. Unless otherwise provided in the applicable prospectus supplement, each series of preferred stock will rank equally as to dividends and liquidation rights in all respects with each other series of preferred stock. The rights of holders of shares of each series of preferred stock will be subordinate to those of our general creditors.

As described under "Description of Depositary Shares," we may, at our option, with respect to any series of preferred stock, elect to offer fractional interests in shares of preferred stock, and provide for the issuance of depositary receipts representing depositary shares, each of which will represent a fractional interest in a share of the series of preferred stock. The fractional interest will be specified in the prospectus supplement relating to a particular series of preferred stock.

Rank. Unless otherwise provided in the applicable prospectus supplement, the preferred stock will, with respect to dividend rights and rights upon our liquidation, dissolution or winding up of our affairs, rank:

- senior to our common stock and to all equity securities ranking junior to such preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs;
- on a parity with all equity securities issued by us, the terms of which specifically provide that such equity securities rank on a parity with the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs; and
- junior to all equity securities issued by us, the terms of which specifically provide that such equity securities rank senior to the preferred stock with respect to dividend rights or rights upon our liquidation, dissolution or winding up of our affairs.

The term "equity securities" does not include convertible debt securities.

Dividends. Holders of the preferred stock of each series will be entitled to receive, when, as and if declared by our board of directors, cash dividends at such rates and on such dates described in the prospectus supplement. Different series of preferred stock may be entitled to dividends at different rates or based on different methods of calculation. The dividend rate may be fixed or variable or both. Dividends will be payable to the holders of record as they appear on our stock books on record dates fixed by our board of directors, as specified in the applicable prospectus supplement.

Dividends on any series of preferred stock may be cumulative or noncumulative, as described in the applicable prospectus supplement. If our board of directors does not declare a dividend payable on a dividend payment date on any series of noncumulative preferred stock, then the holders of that noncumulative preferred stock will have no right to receive a dividend for that dividend payment date, and we will have no obligation to pay the dividend accrued for that period, whether or not dividends on that series are declared payable on any future dividend payment dates. Dividends on any series of cumulative preferred stock will accrue from the date we initially issue shares of such series or such other date specified in the applicable prospectus supplement.

No dividends may be declared or paid or funds set apart for the payment of any dividends on any parity securities unless full dividends have been paid or set apart for payment on the preferred stock. If full dividends are not paid, the preferred stock will share dividends pro rata with the parity securities.

No dividends may be declared or paid or funds set apart for the payment of dividends on any junior securities unless full dividends for all dividend periods terminating on or prior to the date of the declaration or payment will have been paid or declared and a sum sufficient for the payment set apart for payment on the preferred stock.

Liquidation Preference. Upon any voluntary or involuntary liquidation, dissolution or winding up of our affairs, then, before we make any distribution or payment to the holders of any common stock or any other class or series of our capital stock ranking junior to the preferred stock in the distribution of assets upon any liquidation, dissolution or winding up of our affairs, the holders of each series of preferred stock shall be entitled to receive out of assets legally available for distribution to stockholders, liquidating distributions in the amount of the liquidation preference per share set forth in

the prospectus supplement, plus any accrued and unpaid dividends thereon. Such dividends will not include any accumulation in respect of unpaid noncumulative dividends for prior dividend periods. Unless otherwise provided in the applicable prospectus supplement, after payment of the full amount of their liquidating distributions, the holders of preferred stock will have no right or claim to any of our remaining assets. Upon any such voluntary or involuntary liquidation, dissolution or winding up, if our available assets are insufficient to pay the amount of the liquidating distributions on all outstanding preferred stock and the corresponding amounts payable on all other classes or series of our capital stock ranking on parity with the preferred stock and all other such classes or series of shares of capital stock ranking on parity with the preferred stock in the distribution of assets, then the holders of the preferred stock and all other such classes or series of capital stock will share ratably in any such distribution of assets in proportion to the full liquidating distributions to which they would otherwise be entitled.

Upon any such liquidation, dissolution or winding up and if we have made liquidating distributions in full to all holders of preferred stock, we will distribute our remaining assets among the holders of any other classes or series of capital stock ranking junior to the preferred stock according to their respective rights and preferences and, in each case, according to their respective number of shares. For such purposes, our consolidation or merger with or into any other corporation, trust or entity, or the sale, lease or conveyance of all or substantially all of our property or assets will not be deemed to constitute a liquidation, dissolution or winding up of our affairs.

Redemption. If so provided in the applicable prospectus supplement, the preferred stock will be subject to mandatory redemption or redemption at our option, as a whole or in part, in each case upon the terms, at the times and at the redemption prices set forth in such prospectus supplement.

The prospectus supplement relating to a series of preferred stock that is subject to mandatory redemption will specify the number of shares of preferred stock that shall be redeemed by us in each year commencing after a date to be specified, at a redemption price per share to be specified, together with an amount equal to all accrued and unpaid dividends thereon to the date of redemption. Unless the shares have a cumulative dividend, such accrued dividends will not include any accumulation in respect of unpaid dividends for prior dividend periods. We may pay the redemption price in cash or other property, as specified in the applicable prospectus supplement. If the redemption price for preferred stock of any series is payable only from the net proceeds of the issuance of shares of our capital stock, the terms of such preferred stock may provide that, if no such shares of our capital stock shall have been issued or to the extent the net proceeds from any issuance are insufficient to pay in full the aggregate redemption price then due, such preferred stock shall automatically and mandatorily be converted into the applicable shares of our capital stock pursuant to conversion provisions specified in the applicable prospectus supplement. Notwithstanding the foregoing, we will not redeem any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on the preferred stock for all past dividend periods and the then current dividend period; or
- if such series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends for the then current dividend period.

In addition, we will not acquire any preferred stock of a series unless:

- if that series of preferred stock has a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full cumulative dividends on all outstanding shares of such series of preferred stock for all past dividend periods and the then current dividend period; or

- if that series of preferred stock does not have a cumulative dividend, we have declared and paid or contemporaneously declare and pay or set aside funds to pay full dividends on the preferred stock of such series for the then current dividend period.

However, at any time we may purchase or acquire preferred stock of that series (1) pursuant to a purchase or exchange offer made on the same terms to holders of all outstanding preferred stock of such series or (2) by conversion into or exchange for shares of our capital stock ranking junior to the preferred stock of such series as to dividends and upon liquidation.

If fewer than all of the outstanding shares of preferred stock of any series are to be redeemed, we will determine the number of shares that may be redeemed pro rata from the holders of record of such shares in proportion to the number of such shares held or for which redemption is requested by such holder or by any other equitable manner that we determine. Such determination will reflect adjustments to avoid redemption of fractional shares.

Unless otherwise provided in the applicable prospectus supplement, we will mail notice of redemption at least 30 days but not more than 60 days before the redemption date to each holder of record of preferred stock to be redeemed at the address shown on our stock transfer books. Each notice shall state:

- the redemption date;
- the number of shares and series of preferred stock to be redeemed;
- the redemption price;
- the place or places where certificates for such preferred stock are to be surrendered for payment of the redemption price;
- that dividends on the shares to be redeemed will cease to accrue on such redemption date;
- the date on which the holder's conversion rights, if any, as to such shares shall terminate; and
- the specific number of shares to be redeemed from each such holder if fewer than all the shares of any series are to be redeemed.

If notice of redemption has been given and we have set aside the funds necessary for such redemption in trust for the benefit of the holders of any shares called for redemption, then from and after the redemption date, dividends will cease to accrue on such shares, and all rights of the holders of such shares will terminate, except the right to receive the redemption price.

Voting Rights. Holders of preferred stock will not have any voting rights, except as required by law or as indicated in the applicable prospectus supplement.

Unless otherwise provided for under the terms of any series of preferred stock, no consent or vote of the holders of shares of preferred stock or any series thereof shall be required for any amendment to our certificate of incorporation that would increase the number of authorized shares of preferred stock or the number of authorized shares of any series thereof or decrease the number of authorized shares of preferred stock or the number of authorized shares of any series thereof (but not below the number of authorized shares of preferred stock or such series, as the case may be, then outstanding).

Conversion Rights. The terms and conditions, if any, upon which any series of preferred stock is convertible into our common stock will be set forth in the applicable prospectus supplement relating thereto. Such terms will include the number of shares of common stock into which the shares of preferred stock are convertible, the conversion price, rate or manner of calculation thereof, the conversion period, provisions as to whether conversion will be at our option or at the option of the holders of the preferred stock, the events requiring an adjustment of the conversion price and provisions affecting conversion in the event of the redemption.

Transfer Agent and Registrar. The transfer agent and registrar for the preferred stock will be set forth in the applicable prospectus supplement.

Effects of Authorized but Unissued Stock

We have shares of common stock and preferred stock available for future issuance without stockholder approval, subject to any limitations imposed by the listing standards of The NASDAQ Global Select Market. We may utilize these additional shares for a variety of corporate purposes, including for future public offerings to raise additional capital or facilitate corporate acquisitions or for payment as a dividend on our capital stock. The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a controlling interest in our company by means of a merger, tender offer, proxy contest or otherwise. In addition, if we issue preferred stock, the issuance could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation.

Registration Rights

We entered into a second amended and restated investors' rights agreement, dated as of November 7, 2014, which we refer to as the Investors' Rights Agreement, with the holders of shares of our common stock. Under the Investors' Rights Agreement, holders of registrable shares can demand that we file a registration statement or request that their shares be included on a registration statement that we are otherwise filing, in either case, registering the resale of their shares of common stock. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration and our right, in certain circumstances, not to effect a requested registration on Form S-1 within 60 days before or 180 days following any offering of our securities or a requested registration on Form S-3 within 30 days before or 90 days following any offering of our securities. The registration rights will terminate upon the later of the date on which all registrable shares have been sold and May 5, 2020.

Demand Registration Rights. The holders of at least a majority of our registrable shares may require us to file a registration statement under the Securities Act on a Form S-1 or Form S-3, if available, at our expense with respect to the resale of their registrable shares, and we are required to use our best efforts to effect the registration.

Piggyback Registration Rights. If we propose to register any of our securities under the Securities Act for our own account or the account of any other holder, the holders of registrable shares are entitled to notice of such registration and to request that we include registrable shares for resale on such registration statement, subject to the right of any underwriter to limit the number of shares included in such registration.

Expenses. We will pay all registration expenses, other than underwriting discounts and commissions, related to any demand or piggyback registration. The Investors' Rights Agreement contains customary cross-indemnification provisions pursuant to which we are obligated to indemnify the selling stockholders in the event of misstatements or omissions in the registration statement attributable to us except in the event of fraud and they are obligated to indemnify us for misstatements or omissions attributable to them.

Provisions of our Certificate of Incorporation and Bylaws and Delaware Law That May Have Anti-takeover Effects

Our certificate of incorporation and bylaws include a number of provisions that may have the effect of encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board Composition and Filling Vacancies. In accordance with our certificate of incorporation, our board is divided into three classes serving three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office, even if less than a quorum.

No Written Consent of Stockholders. Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting.

Meetings of Stockholders. Our bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements. Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in the bylaws. These provisions may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

Amendment to Certificate of Incorporation and Bylaws. As required by the Delaware General Corporation Law, any amendment of our certificate of incorporation must first be approved by a majority of our board of directors and, if required by law or our certificate of incorporation, thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, directors, limitation of liability, exclusive jurisdiction of Delaware Courts and the amendment of our bylaws and certificate of incorporation must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the bylaws; and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment, or, if the board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

Blank Check Preferred Stock. Our certificate of incorporation provides for 5,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Section 203 of the Delaware General Corporation Law. We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. An "interested stockholder" is a person who, together with affiliates and associates, owns, or did own within three years prior to the determination of interested stockholder status, 15% or more of the corporation's voting stock. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, the board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances; or
- at or after the time the stockholder became interested, the business combination was approved by the board of directors of the corporation and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

A Delaware corporation may "opt out" of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or bylaws resulting from a stockholders' amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Exclusive Jurisdiction of Certain Actions. Our certificate of incorporation requires, to the fullest extent permitted by law, that derivative actions brought in our name, actions against our directors, officers and employees for breach of fiduciary duty and other similar actions may be brought only in the Court of Chancery in the State of Delaware, unless we otherwise consent. Although we believe this provision benefits us by providing increased consistency in the application of Delaware law in the types of lawsuits to which it applies, the provision may have the effect of discouraging lawsuits against our directors and officers.

DESCRIPTION OF DEBT SECURITIES

We may offer debt securities which may be senior or subordinated. We refer to the senior debt securities and the subordinated debt securities collectively as debt securities. The following description summarizes the general terms and provisions of the debt securities. We will describe the specific terms of the debt securities and the extent, if any, to which the general provisions summarized below apply to any series of debt securities in the prospectus supplement relating to the series and any applicable free writing prospectus that we authorize to be delivered. When we refer to "the Company," "we," "our," and "us" in this section, we mean Blueprint Medicines Corporation excluding, unless the context otherwise requires or as otherwise expressly stated, our subsidiaries.

We may issue senior debt securities from time to time, in one or more series under a senior indenture to be entered into between us and a senior trustee to be named in a prospectus supplement, which we refer to as the senior trustee. We may issue subordinated debt securities from time to time, in one or more series under a subordinated indenture to be entered into between us and a subordinated trustee to be named in a prospectus supplement, which we refer to as the subordinated trustee. The forms of senior indenture and subordinated indenture are filed as exhibits to the registration statement of which this prospectus forms a part. Together, the senior indenture and the subordinated indenture are referred to as the indentures and, together, the senior trustee and the subordinated trustee are referred to as the trustees. This prospectus briefly outlines some of the provisions of the indentures. The following summary of the material provisions of the indentures is qualified in its entirety by the provisions of the indentures, including definitions of certain terms used in the indentures. Wherever we refer to particular sections or defined terms of the indentures, those sections or defined terms are incorporated by reference in this prospectus or the applicable prospectus supplement. You should review the indentures that are filed as exhibits to the registration statement of which this prospectus forms a part for additional information. As used in this prospectus, the term "debt securities" includes the debt securities being offered by this prospectus and all other debt securities issued by us under the indentures.

General

The indentures:

- do not limit the amount of debt securities that we may issue;
- allow us to issue debt securities in one or more series;
- do not require us to issue all of the debt securities of a series at the same time;
- allow us to reopen a series to issue additional debt securities without the consent of the holders of the debt securities of such series; and
- provide that the debt securities will be unsecured, except as may be set forth in the applicable prospectus supplement.

Unless otherwise provided in the applicable prospectus supplement, the senior debt securities will be unsubordinated obligations and will rank equally with all of our other unsecured and unsubordinated indebtedness. Payments on the subordinated debt securities will be subordinated to the prior payment in full of all of our senior indebtedness, as described under "—Subordination" and in the applicable prospectus supplement.

Each indenture provides that we may, but need not, designate more than one trustee under an indenture. Any trustee under an indenture may resign or be removed and a successor trustee may be appointed to act with respect to the series of debt securities administered by the resigning or removed trustee. If two or more persons are acting as trustee with respect to different series of debt securities, each trustee shall be a trustee of a trust under the applicable indenture separate and apart from the

trust administered by any other trustee. Except as otherwise indicated in this prospectus, any action described in this prospectus to be taken by each trustee may be taken by each trustee with respect to, and only with respect to, the one or more series of debt securities for which it is trustee under the applicable indenture.

The prospectus supplement for each offering will provide the following terms, where applicable:

- the title of the debt securities and whether they are senior or subordinated;
- the aggregate principal amount of the debt securities being offered, the aggregate principal amount of the debt securities outstanding as of the most recent practicable date and any limit on their aggregate principal amount, including the aggregate principal amount of debt securities authorized;
- the price at which the debt securities will be issued, expressed as a percentage of the principal and, if other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof or, if applicable, the portion of the principal amount of such debt securities that is convertible into common stock or other securities of ours or the method by which any such portion shall be determined;
- if convertible, the terms on which such debt securities are convertible, including the initial conversion price or rate and the conversion period and any applicable limitations on the ownership or transferability of common stock or other securities of ours received on conversion;
- the date or dates, or the method for determining the date or dates, on which the principal of the debt securities will be payable;
- the fixed or variable interest rate or rates of the debt securities, or the method by which the interest rate or rates is determined;
- the date or dates, or the method for determining the date or dates, from which interest will accrue;
- the dates on which interest will be payable;
- the record dates for interest payment dates, or the method by which such dates will be determine;
- the persons to whom interest will be payable;
- the basis upon which interest will be calculated if other than that of a 360-day year of twelve 30-day months;
- any make-whole amount, which is the amount in addition to principal and interest that is required to be paid to the holder of a debt security as a result of any optional redemption or accelerated payment of such debt security, or the method for determining the make-whole amount;
- the place or places where the principal of, and any premium or make-whole amount, and interest on, the debt securities will be payable;
- where the debt securities may be surrendered for registration of transfer or conversion or exchange;
- where notices or demands to or upon us in respect of the debt securities and the applicable indenture may be served;
- the times, prices and other terms and conditions upon which we may redeem the debt securities;

- any obligation we have to redeem, repay or purchase the debt securities pursuant to any sinking fund or analogous provision or at the option of holders of the debt securities, and the times and prices at which we must redeem, repay or purchase the debt securities as a result of such obligation;
- the currency or currencies in which the debt securities are denominated and payable if other than United States dollars, which may be a foreign currency or units of two or more foreign currencies or a composite currency or currencies and the terms and conditions relating thereto, and the manner of determining the equivalent of such foreign currency in United States dollars;
- whether the principal of, and any premium or make-whole amount, or interest on, the debt securities of the series are to be payable, at our election or at the election of a holder, in a currency or currencies other than that in which the debt securities are denominated or stated to be payable, and other related terms and conditions;
- whether the amount of payments of principal of, and any premium or make-whole amount, or interest on, the debt securities may be determined according to an index, formula or other method and how such amounts will be determined;
- whether the debt securities will be in registered form, bearer form, or both, and (i) if in registered form, the person to whom any interest shall be payable, if other than the person in whose name the security is registered at the close of business on the regular record date for such interest, or (ii) if in bearer form, the manner in which, or the person to whom, any interest on the security shall be payable if otherwise than upon presentation and surrender upon maturity;
- any restrictions applicable to the offer, sale or delivery of securities in bearer form and the terms upon which securities in bearer form of the series may be exchanged for securities in registered form of the series and vice versa, if permitted by applicable laws and regulations;
- whether any debt securities of the series are to be issuable initially in temporary global form and whether any debt securities of the series are to be issuable in permanent global form with or without coupons and, if so, whether beneficial owners of interests in any such permanent global security may, or shall be required to, exchange their interests for other debt securities of the series, and the manner in which interest shall be paid;
- the identity of the depositary for securities in registered form, if such series are to be issuable as a global security;
- the date as of which any debt securities in bearer form or in temporary global form shall be dated if other than the original issuance date of the first security of the series to be issued;
- the applicability, if any, of the defeasance and covenant defeasance provisions described in this prospectus or in the applicable indenture;
- whether and under what circumstances we will pay any additional amounts on the debt securities in respect of any tax, assessment or governmental charge and, if so, whether we will have the option to redeem the debt securities in lieu of making such a payment;
- whether and under what circumstances the debt securities being offered are convertible into common stock or other securities of ours, as the case may be, including the conversion price or rate and the manner or calculation thereof;
- the circumstances, if any, specified in the applicable prospectus supplement, under which beneficial owners of interests in the global security may obtain definitive debt securities and the manner in which payments on a permanent global debt security will be made if any debt securities are issuable in temporary or permanent global form;

- any provisions granting special rights to holders of securities upon the occurrence of such events as specified in the applicable prospectus supplement;
- if the debt securities of such series are to be issuable in definitive form only upon receipt of certain certificates or other documents or satisfaction of other conditions, then the form and/or terms of such certificates, documents or conditions;
- the name of the applicable trustee and the nature of any material relationship with us or any of our affiliates, and the percentage of debt securities of the class necessary to require the trustee to take action;
- any deletions from, modifications of or additions to our events of default or covenants with regard to such debt securities and any change in the right of any trustee or any of the holders to declare the principal amount of any of such debt securities due and payable;
- applicable CUSIP numbers; and
- any other terms of such debt securities not inconsistent with the provisions of the applicable indenture.

We may issue debt securities that provide for less than the entire principal amount thereof to be payable upon declaration of acceleration of the maturity of the debt securities. We refer to any such debt securities throughout this prospectus as "original issue discount securities." The applicable prospectus supplement will describe the United States federal income tax consequences and other relevant considerations applicable to original issue discount securities.

We also may issue indexed debt securities. Payments of principal of, and premium and interest on, indexed debt securities are determined with reference to the rate of exchange between the currency or currency unit in which the debt security is denominated and any other currency or currency unit specified by us, to the relationship between two or more currencies or currency units or by other similar methods or formulas specified in the prospectus supplement.

Except as described under "—Merger, Consolidation or Sale of Assets" or as may be set forth in any prospectus supplement, the debt securities will not contain any provisions that (i) would limit our ability to incur indebtedness or (ii) would afford holders of debt securities protection in the event of (a) a highly leveraged or similar transaction involving us, or (b) a change of control or reorganization, restructuring, merger or similar transaction involving us that may adversely affect the holders of the debt securities. In the future, we may enter into transactions, such as the sale of all or substantially all of our assets or a merger or consolidation, that may have an adverse effect on our ability to service our indebtedness, including the debt securities, by, among other things, substantially reducing or eliminating our assets.

Our governing instruments do not define the term "substantially all" as it relates to the sale of assets. Additionally, Delaware cases interpreting the term "substantially all" rely upon the facts and circumstances of each particular case. Consequently, to determine whether a sale of "substantially all" of our assets has occurred, a holder of debt securities must review the financial and other information that we have disclosed to the public.

We will provide you with more information in the applicable prospectus supplement regarding any deletions, modifications, or additions to the events of default or covenants that are described below, including any addition of a covenant or other provision providing event risk or similar protection.

Payment

Unless otherwise provided in the applicable prospectus supplement, the principal of, and any premium or make-whole amount, and interest on, any series of the debt securities will be payable at

the corporate trust office of the trustee. We will provide you with the address of the trustee in the applicable prospectus supplement. We may also pay interest by mailing a check to the address of the person entitled to it as it appears in the applicable register for the debt securities or by wire transfer of funds to that person at an account maintained within the United States.

All monies that we pay to a paying agent or a trustee for the payment of the principal of, and any premium or make-whole amount, or interest on, any debt security will be repaid to us if unclaimed at the end of two years after the obligation underlying payment becomes due and payable. After funds have been returned to us, the holder of the debt security may look only to us for payment, without payment of interest for the period which we hold the funds.

Denomination, Interest, Registration and Transfer

Unless otherwise provided in the applicable prospectus supplement, the debt securities of any series will be issuable in denominations of \$1,000 and integral multiples of \$1,000.

Subject to the limitations imposed upon debt securities that are evidenced by a computerized entry in the records of a depository company rather than by physical delivery of a note, a holder of debt securities of any series may:

- exchange them for any authorized denomination of other debt securities of the same series and of a like aggregate principal amount and kind upon surrender of such debt securities at the corporate trust office of the applicable trustee or at the office of any transfer agent that we designate for such purpose; and
- surrender them for registration of transfer or exchange at the corporate trust office of the applicable trustee or at the office of any transfer agent that we designate for such purpose.

Every debt security surrendered for registration of transfer or exchange must be duly endorsed or accompanied by a written instrument of transfer satisfactory to the applicable trustee or transfer agent. Payment of a service charge will not be required for any registration of transfer or exchange of any debt securities, but we or the trustee may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection therewith. If in addition to the applicable trustee, the applicable prospectus supplement refers to any transfer agent initially designated by us for any series of debt securities, we may at any time rescind the designation of any such transfer agent or approve a change in the location through which any such transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for such series. We may at any time designate additional transfer agents for any series of debt securities.

Neither we, nor any trustee, will be required to:

- issue, register the transfer of or exchange debt securities of any series during a period beginning at the opening of business 15 days before the day that the notice of redemption of any debt securities selected for redemption is mailed and ending at the close of business on the day of such mailing;
- register the transfer of or exchange any debt security, or portion thereof, so selected for redemption, in whole or in part, except the unredeemed portion of any debt security being redeemed in part; and
- issue, register the transfer of or exchange any debt security that has been surrendered for repayment at the option of the holder, except the portion, if any, of such debt security not to be so repaid.

Merger, Consolidation or Sale of Assets

The indentures provide that we may, without the consent of the holders of any outstanding debt securities, (i) consolidate with, (ii) sell, lease or convey all or substantially all of our assets to, or (iii) merge with or into, any other entity provided that:

- either we are the continuing entity, or the successor entity, if other than us, assumes the obligations (a) to pay the principal of, and any premium or make-whole amount, and interest on, all of the debt securities and (b) to duly perform and observe all of the covenants and conditions contained in each indenture;
- after giving effect to the transaction, there is no event of default under the indentures and no event which, after notice or the lapse of time, or both, would become such an event of default, occurs and continues; and
- an officers' certificate and legal opinion covering such conditions are delivered to each applicable trustee.

Covenants

Existence. Except as described under "—Merger, Consolidation or Sale of Assets," the indentures require us to do or cause to be done all things necessary to preserve and keep in full force and effect our existence, rights and franchises. However, the indentures do not require us to preserve any right or franchise if we determine that any right or franchise is no longer desirable in the conduct of our business.

Payment of taxes and other claims. The indentures require us to pay, discharge or cause to be paid or discharged, before they become delinquent (i) all taxes, assessments and governmental charges levied or imposed on us, our subsidiaries or our subsidiaries' income, profits or property, and (ii) all lawful claims for labor, materials and supplies which, if unpaid, might by law become a lien upon our property or the property of our subsidiaries. However, we will not be required to pay, discharge or cause to be paid or discharged any such tax, assessment, charge or claim whose amount, applicability or validity is being contested in good faith by appropriate proceedings.

Provision of financial information. The indentures require us to (i) within 15 days of each of the respective dates by which we are required to file our annual reports, quarterly reports and other documents with the SEC, file with the trustee copies of the annual report, quarterly report and other documents that we file with the SEC under Section 13 or 15(d) of the Exchange Act, (ii) file with the trustee and the SEC any additional information, documents and reports regarding compliance by us with the conditions and covenants of the indentures, as required, (iii) within 30 days after the filing with the trustee, mail to all holders of debt securities, as their names and addresses appear in the applicable register for such debt securities, without cost to such holders, summaries of any documents and reports required to be filed by us pursuant to (i) and (ii) above, and (iv) supply, promptly upon written request and payment of the reasonable cost of duplication and delivery, copies of such documents to any prospective holder.

Additional covenants. The applicable prospectus supplement will set forth any additional covenants relating to any series of debt securities.

Events of Default, Notice and Waiver

Unless the applicable prospectus supplement states otherwise, when we refer to "events of default" as defined in the indentures with respect to any series of debt securities, we mean:

- default in the payment of any installment of interest on any debt security of such series continuing for 30 days;
- default in the payment of principal of, or any premium or make-whole amount on, any debt security of such series for five business days at its stated maturity;
- default in making any sinking fund payment as required for any debt security of such series for five business days;
- default in the performance or breach of any covenant or warranty in the debt securities or in the indenture by us continuing for 60 days after written notice as provided in the applicable indenture, but not of a covenant added to the indenture solely for the benefit of a series of debt securities issued thereunder other than such series;
- a default under any bond, debenture, note, mortgage, indenture or instrument: (i) having an aggregate principal amount of at least \$30,000,000; or (ii) under which there may be issued, secured or evidenced any existing or later created indebtedness for money borrowed by us or our subsidiaries, if we are directly responsible or liable as obligor or guarantor,

if the default results in the indebtedness becoming or being declared due and payable prior to the date it otherwise would have, without such indebtedness having been discharged, or such acceleration having been rescinded or annulled, within 30 days after notice to the issuing company specifying such default. Such notice shall be given to us by the trustee, or to us and the trustee by the holders of at least 10% in principal amount of the outstanding debt securities of that series. The written notice shall specify such default and require us to cause such indebtedness to be discharged or cause such acceleration to be rescinded or annulled and shall state that such notice is a "Notice of Default" under such indenture;

- bankruptcy, insolvency or reorganization, or court appointment of a receiver, liquidator or trustee of us or any significant subsidiary of ours; and
- any other event of default provided with respect to a particular series of debt securities.

When we use the term "significant subsidiary," we refer to the meaning ascribed to such term in Rule 1-02 of Regulation S-X promulgated under the Securities Act.

If an event of default occurs and is continuing with respect to debt securities of any series outstanding, then the applicable trustee or the holders of 25% or more in principal amount of the debt securities of that series will have the right to declare the principal amount of all the debt securities of that series to be due and payable. If the debt securities of that series are original issue discount securities or indexed securities, then the applicable trustee or the holders of 25% or more in principal amount of the debt securities of that series will have the right to declare the portion of the principal amount as may be specified in the terms thereof to be due and payable. However, at any time after such a declaration of acceleration has been made, but before a judgment or decree for payment of the money due has been obtained by the applicable trustee, the holders of at least a majority in principal amount of outstanding debt securities of such series or of all debt securities then outstanding under the applicable indenture may rescind and annul such declaration and its consequences if:

- we have deposited with the applicable trustee all required payments of the principal, any premium or make-whole amount, interest and, to the extent permitted by law, interest on overdue installment of interest, plus applicable fees, expenses, disbursements and advances of the applicable trustee; and

- all events of default, other than the non-payment of accelerated principal, or a specified portion thereof, and any premium or make-whole amount, have been cured or waived.

The indentures also provide that the holders of at least a majority in principal amount of the outstanding debt securities of any series or of all debt securities then outstanding under the applicable indenture may, on behalf of all holders, waive any past default with respect to such series and its consequences, except a default:

- in the payment of the principal, any premium or make-whole amount, or interest;
- in respect of a covenant or provision contained in the applicable indenture that cannot be modified or amended without the consent of the holders of the outstanding debt security that is affected by the default; or
- in respect of a covenant or provision for the benefit or protection of the trustee, without its express written consent.

The indentures require each trustee to give notice to the holders of debt securities within 90 days of a default unless such default has been cured or waived. However, the trustee may withhold notice if specified persons of such trustee consider such withholding to be in the interest of the holders of debt securities. The trustee may not withhold notice of a default in the payment of principal, any premium or interest on any debt security of such series or in the payment of any sinking fund installment in respect of any debt security of such series.

The indentures provide that holders of debt securities of any series may not institute any proceedings, judicial or otherwise, with respect to such indenture or for any remedy under the indenture, unless the trustee fails to act for a period of 60 days after the trustee has received a written request to institute proceedings in respect of an event of default from the holders of 25% or more in principal amount of the outstanding debt securities of such series, as well as an offer of indemnity reasonably satisfactory to the trustee. However, this provision will not prevent any holder of debt securities from instituting suit for the enforcement of payment of the principal of, and any premium or make-whole amount, and interest on, such debt securities at the respective due dates thereof.

The indentures provide that, subject to provisions in each indenture relating to its duties in the case of a default, a trustee has no obligation to exercise any of its rights or powers at the request or direction of any holders of any series of debt securities then outstanding under the indenture, unless the holders have offered to the trustee reasonable security or indemnity. The holders of at least a majority in principal amount of the outstanding debt securities of any series or of all debt securities then outstanding under an indenture shall have the right to direct the time, method and place of conducting any proceeding for any remedy available to the applicable trustee, or of exercising any trust or power conferred upon such trustee. However, a trustee may refuse to follow any direction which:

- is in conflict with any law or the applicable indenture;
- may involve the trustee in personal liability; or
- may be unduly prejudicial to the holders of debt securities of the series not joining the proceeding.

Within 120 days after the close of each fiscal year, we will be required to deliver to each trustee a certificate, signed by one of our several specified officers, stating whether or not that officer has knowledge of any default under the applicable indenture. If the officer has knowledge of any default, the notice must specify the nature and status of the default.

Modification of the Indentures

The indentures provide that modifications and amendments may be made only with the consent of the affected holders of a majority in principal amount of all outstanding debt securities issued under that indenture. However, no such modification or amendment may, without the consent of the holders of the debt securities affected by the modification or amendment:

- change the stated maturity of the principal of, or any premium or make-whole amount on, or any installment of principal of or interest on, any such debt security;
- reduce the principal amount of, the rate or amount of interest on, or any premium or make-whole amount payable on redemption of, any such debt security;
- reduce the amount of principal of an original issue discount security that would be due and payable upon declaration of acceleration of the maturity thereof or would be provable in bankruptcy, or adversely affect any right of repayment of the holder of any such debt security;
- change the place of payment or the coin or currency for payment of principal of, or any premium or make-whole amount, or interest on, any such debt security;
- impair the right to institute suit for the enforcement of any payment on or with respect to any such debt security;
- reduce the percentage in principal amount of any outstanding debt securities necessary to modify or amend the applicable indenture with respect to such debt securities, to waive compliance with particular provisions thereof or defaults and consequences thereunder or to reduce the quorum or voting requirements set forth in the applicable indenture; and
- modify any of the foregoing provisions or any of the provisions relating to the waiver of particular past defaults or covenants, except to increase the required percentage to effect such action or to provide that some of the other provisions may not be modified or waived without the consent of the holder of such debt security.

The holders of a majority in aggregate principal amount of the outstanding debt securities of each series may, on behalf of all holders of debt securities of that series, waive, insofar as that series is concerned, our compliance with material restrictive covenants of the applicable indenture.

We and our respective trustee may make modifications and amendments of an indenture without the consent of any holder of debt securities for any of the following purposes:

- to evidence the succession of another person to us as obligor under such indenture;
- to add to our covenants for the benefit of the holders of all or any series of debt securities or to surrender any right or power conferred upon us in such indenture;
- to add events of default for the benefit of the holders of all or any series of debt securities;
- to add or change any provisions of an indenture (i) to change or eliminate restrictions on the payment of principal of, or premium or make-whole amount, or interest on, debt securities in bearer form, or (ii) to permit or facilitate the issuance of debt securities in uncertificated form, provided that such action shall not adversely affect the interests of the holders of the debt securities of any series in any material respect;
- to change or eliminate any provisions of an indenture, provided that any such change or elimination shall become effective only when there are no debt securities outstanding of any series created prior thereto which are entitled to the benefit of such provision;
- to secure the debt securities;

- to establish the form or terms of debt securities of any series;
- to provide for the acceptance of appointment by a successor trustee or facilitate the administration of the trusts under an indenture by more than one trustee;
- to cure any ambiguity, defect or inconsistency in an indenture, provided that such action shall not adversely affect the interests of holders of debt securities of any series issued under such indenture; and
- to supplement any of the provisions of an indenture to the extent necessary to permit or facilitate defeasance and discharge of any series of such debt securities, provided that such action shall not adversely affect the interests of the holders of the outstanding debt securities of any series.

Voting

The indentures provide that in determining whether the holders of the requisite principal amount of outstanding debt securities of a series have given any request, demand, authorization, direction, notice, consent or waiver under the indentures or whether a quorum is present at a meeting of holders of debt securities:

- the principal amount of an original issue discount security that shall be deemed to be outstanding shall be the amount of the principal thereof that would be due and payable as of the date of such determination upon declaration of acceleration of the maturity thereof;
- the principal amount of any debt security denominated in a foreign currency that shall be deemed outstanding shall be the United States dollar equivalent, determined on the issue date for such debt security, of the principal amount or, in the case of an original issue discount security, the United States dollar equivalent on the issue date of such debt security of the amount determined as provided in the preceding bullet point;
- the principal amount of an indexed security that shall be deemed outstanding shall be the principal face amount of such indexed security at original issuance, unless otherwise provided for such indexed security under such indenture; and
- debt securities owned by us or any other obligor upon the debt securities or by any affiliate of ours or of such other obligor shall be disregarded.

The indentures contain provisions for convening meetings of the holders of debt securities of a series. A meeting will be permitted to be called at any time by the applicable trustee, and also, upon request, by us or the holders of at least 25% in principal amount of the outstanding debt securities of such series, in any such case upon notice given as provided in such indenture. Except for any consent that must be given by the holder of each debt security affected by the modifications and amendments of an indenture described above, any resolution presented at a meeting or adjourned meeting duly reconvened at which a quorum is present may be adopted by the affirmative vote of the holders of a majority of the aggregate principal amount of the outstanding debt securities of that series represented at such meeting.

Notwithstanding the preceding paragraph, except as referred to above, any resolution relating to a request, demand, authorization, direction, notice, consent, waiver or other action that may be made, given or taken by the holders of a specified percentage, which is less than a majority of the aggregate principal amount of the outstanding debt securities of a series, may be adopted at a meeting or adjourned meeting duly reconvened at which a quorum is present by the affirmative vote of such specified percentage.

Any resolution passed or decision taken at any properly held meeting of holders of debt securities of any series will be binding on all holders of such series. The quorum at any meeting called to adopt a resolution, and at any reconvened meeting, will be persons holding or representing a majority in principal amount of the outstanding debt securities of a series. However, if any action is to be taken relating to a consent or waiver which may be given by the holders of at least a specified percentage in principal amount of the outstanding debt securities of a series, the persons holding such percentage will constitute a quorum.

Notwithstanding the foregoing provisions, the indentures provide that if any action is to be taken at a meeting with respect to any request, demand, authorization, direction, notice, consent, waiver or other action that such indenture expressly provides may be made, given or taken by the holders of a specified percentage in principal amount of all outstanding debt securities affected by such action, or of the holders of such series and one or more additional series:

- there shall be no minimum quorum requirement for such meeting; and
- the principal amount of the outstanding debt securities of such series that vote in favor of such request, demand, authorization, direction, notice, consent, waiver or other action shall be taken account in determining whether such request, demand, authorization, direction, notice, consent, waiver or other action has been made, given or taken under such indenture.

Subordination

Unless otherwise provided in the applicable prospectus supplement, subordinated debt securities will be subject to the following subordination provisions.

Upon any distribution to our creditors in a liquidation, dissolution or reorganization, the payment of the principal of and interest on any subordinated debt securities will be subordinated to the extent provided in the applicable indenture in right of payment to the prior payment in full of all senior debt. However, our obligation to make payments of the principal of and interest on such subordinated debt securities otherwise will not be affected. No payment of principal or interest will be permitted to be made on subordinated debt securities at any time if a default on senior debt exists that permits the holders of such senior debt to accelerate its maturity and the default is the subject of judicial proceedings or we receive notice of the default. After all senior debt is paid in full and until the subordinated debt securities are paid in full, holders of subordinated debt securities will be subrogated to the rights of holders of senior debt to the extent that distributions otherwise payable to holders of subordinated debt securities have been applied to the payment of senior debt. The subordinated indenture will not restrict the amount of senior debt or other indebtedness of ours and our subsidiaries. As a result of these subordination provisions, in the event of a distribution of assets upon insolvency, holders of subordinated debt securities may recover less, ratably, than our general creditors.

The term "senior debt" will be defined in the applicable indenture as the principal of and interest on, or substantially similar payments to be made by us in respect of, other outstanding indebtedness, whether outstanding at the date of execution of the applicable indenture or subsequently incurred, created or assumed. The prospectus supplement may include a description of additional terms implementing the subordination feature.

No restrictions will be included in any indenture relating to subordinated debt securities upon the creation of additional senior debt.

If this prospectus is being delivered in connection with the offering of a series of subordinated debt securities, the accompanying prospectus supplement or the information incorporated in this prospectus by reference will set forth the approximate amount of senior debt outstanding as of the end of our most recent fiscal quarter.

Discharge, Defeasance and Covenant Defeasance

Unless otherwise provided in the applicable prospectus supplement, the indentures allow us to discharge our obligations to holders of any series of debt securities issued under any indenture when:

- either (i) all securities of such series have already been delivered to the applicable trustee for cancellation; or (ii) all securities of such series have not already been delivered to the applicable trustee for cancellation but (a) have become due and payable, (b) will become due and payable within one year, or (c) if redeemable at our option, are to be redeemed within one year, and we have irrevocably deposited with the applicable trustee, in trust, funds in such currency or currencies, currency unit or units or composite currency or currencies in which such debt securities are payable, an amount sufficient to pay the entire indebtedness on such debt securities in respect of principal and any premium or make-whole amount, and interest to the date of such deposit if such debt securities have become due and payable or, if they have not, to the stated maturity or redemption date;
- we have paid or caused to be paid all other sums payable; and
- an officers' certificate and an opinion of counsel stating the conditions to discharging the debt securities have been satisfied has been delivered to the trustee.

Unless otherwise provided in the applicable prospectus supplement, the indentures provide that, upon our irrevocable deposit with the applicable trustee, in trust, of an amount, in such currency or currencies, currency unit or units or composite currency or currencies in which such debt securities are payable at stated maturity, or government obligations, or both, applicable to such debt securities, which through the scheduled payment of principal and interest in accordance with their terms will provide money in an amount sufficient to pay the principal of, and any premium or make-whole amount, and interest on, such debt securities, and any mandatory sinking fund or analogous payments thereon, on the scheduled due dates therefor, the issuing company may elect either:

- to defease and be discharged from any and all obligations with respect to such debt securities; or
- to be released from its obligations with respect to such debt securities under the applicable indenture or, if provided in the applicable prospectus supplement, its obligations with respect to any other covenant, and any omission to comply with such obligations shall not constitute an event of default with respect to such debt securities.

Notwithstanding the above, we may not elect to defease and be discharged from the obligation to pay any additional amounts upon the occurrence of particular events of tax, assessment or governmental charge with respect to payments on such debt securities and the obligations to register the transfer or exchange of such debt securities, to replace temporary or mutilated, destroyed, lost or stolen debt securities, to maintain an office or agency in respect of such debt securities, or to hold monies for payment in trust.

The indentures only permit us to establish the trust described in the paragraph above if, among other things, we have delivered to the applicable trustee an opinion of counsel to the effect that the holders of such debt securities will not recognize income, gain or loss for United States federal income tax purposes as a result of such defeasance or covenant defeasance and will be subject to United States federal income tax on the same amounts, in the same manner and at the same times as would have been the case if such defeasance or covenant defeasance had not occurred. Such opinion of counsel, in the case of defeasance, will be required to refer to and be based upon a ruling received from or published by the Internal Revenue Service or a change in applicable United States federal income tax law occurring after the date of the indenture. In the event of such defeasance, the holders of such debt securities would be able to look only to such trust fund for payment of principal, any premium or make-whole amount, and interest.

When we use the term "government obligations," we mean securities that are:

- direct obligations of the United States or the government that issued the foreign currency in which the debt securities of a particular series are payable, for the payment of which its full faith and credit is pledged; or
- obligations of a person controlled or supervised by and acting as an agency or instrumentality of the United States or other government that issued the foreign currency in which the debt securities of such series are payable, the payment of which is unconditionally guaranteed as a full faith and credit obligation by the United States or such other government, which are not callable or redeemable at the option of the issuer thereof and shall also include a depository receipt issued by a bank or trust company as custodian with respect to any such government obligation or a specific payment of interest on or principal of any such government obligation held by such custodian for the account of the holder of a depository receipt. However, except as required by law, such custodian is not authorized to make any deduction from the amount payable to the holder of such depository receipt from any amount received by the custodian in respect of the government obligation or the specific payment of interest on or principal of the government obligation evidenced by such depository receipt.

Unless otherwise provided in the applicable prospectus supplement, if after we have deposited funds and/or government obligations to effect defeasance or covenant defeasance with respect to debt securities of any series, (i) the holder of a debt security of such series is entitled to, and does, elect under the terms of the applicable indenture or the terms of such debt security to receive payment in a currency, currency unit or composite currency other than that in which such deposit has been made in respect of such debt security, or (ii) a conversion event occurs in respect of the currency, currency unit or composite currency in which such deposit has been made, the indebtedness represented by such debt security will be deemed to have been, and will be, fully discharged and satisfied through the payment of the principal of, and premium or make-whole amount, and interest on, such debt security as they become due out of the proceeds yielded by converting the amount so deposited in respect of such debt security into the currency, currency unit or composite currency in which such debt security becomes payable as a result of such election or such cessation of usage based on the applicable market exchange rate.

When we use the term "conversion event," we mean the cessation of use of:

- a currency, currency unit or composite currency both by the government of the country that issued such currency and for the settlement of transactions by a central bank or other public institutions of or within the international banking community;
- the European Currency Unit both within the European Monetary System and for the settlement of transactions by public institutions of or within the European Communities; or
- any currency unit or composite currency other than the European Currency Unit for the purposes for which it was established.

Unless otherwise provided in the applicable prospectus supplement, all payments of principal of, and any premium or make-whole amount, and interest on, any debt security that is payable in a foreign currency that ceases to be used by its government of issuance shall be made in United States dollars.

In the event that (i) we effect covenant defeasance with respect to any debt securities and (ii) those debt securities are declared due and payable because of the occurrence of any event of default, the amount in the currency, currency unit or composite currency in which such debt securities are payable, and government obligations on deposit with the applicable trustee, will be sufficient to pay amounts due on such debt securities at the time of their stated maturity but may not be sufficient to pay amounts due on such debt securities at the time of the acceleration resulting from such event of

default. However, the issuing company would remain liable to make payments of any amounts due at the time of acceleration.

The applicable prospectus supplement may further describe the provisions, if any, permitting such defeasance or covenant defeasance, including any modifications to the provisions described above, with respect to the debt securities of or within a particular series.

No Recourse

No recourse shall be had under any obligation, covenant or agreement of ours in the senior indenture or any supplemental indenture, or in any of the debt securities or because of the creation of any indebtedness represented thereby, against any of our incorporators, stockholders, officers or directors, past, present or future, or of any predecessor or successor entity thereof under any law, statute or constitutional provision or by the enforcement of any assessment or by any legal or equitable proceeding or otherwise. Each holder, by accepting the debt securities, waives and releases all such liability.

DESCRIPTION OF DEPOSITARY SHARES

General

We may, at our option, elect to offer fractional shares of preferred stock, which we call depositary shares, rather than full shares of preferred stock. If we do, we will issue to the public receipts, called depositary receipts, for depositary shares, each of which will represent a fraction, to be described in the applicable prospectus supplement, of a share of a particular series of preferred stock. Unless otherwise provided in the applicable prospectus supplement, each owner of a depositary share will be entitled, in proportion to the applicable fractional interest in a share of preferred stock represented by the depositary share, to all the rights and preferences of the preferred stock represented by the depositary share. Those rights include dividend, voting, redemption, conversion and liquidation rights.

The shares of preferred stock underlying the depositary shares will be deposited with a bank or trust company selected by us to act as depositary under a deposit agreement between us, the depositary and the holders of the depositary receipts. The depositary will be the transfer agent, registrar and dividend disbursing agent for the depositary shares.

The depositary shares will be evidenced by depositary receipts issued pursuant to the deposit agreement. Holders of depositary receipts agree to be bound by the deposit agreement, which requires holders to take certain actions such as filing proof of residence and paying certain charges.

The summary of terms of the depositary shares contained in this prospectus is not complete. You should refer to the form of the deposit agreement, our certificate of incorporation and the certificate of designation for the applicable series of preferred stock that are, or will be, filed with the SEC.

Dividends and Other Distributions

The depositary will distribute all cash dividends or other cash distributions, if any, received in respect of the preferred stock underlying the depositary shares to the record holders of depositary shares in proportion to the numbers of depositary shares owned by those holders on the relevant record date. The relevant record date for depositary shares will be the same date as the record date for the underlying preferred stock.

If there is a distribution other than in cash, the depositary will distribute property (including securities) received by it to the record holders of depositary shares, unless the depositary determines that it is not feasible to make the distribution. If this occurs, the depositary may, with our approval, adopt another method for the distribution, including selling the property and distributing the net proceeds from the sale to the holders.

Liquidation Preference

If a series of preferred stock underlying the depositary shares has a liquidation preference, in the event of the voluntary or involuntary liquidation, dissolution or winding up of us, holders of depositary shares will be entitled to receive the fraction of the liquidation preference accorded each share of the applicable series of preferred stock, as set forth in the applicable prospectus supplement.

Withdrawal of Stock

Unless the related depositary shares have been previously called for redemption, upon surrender of the depositary receipts at the office of the depositary, the holder of the depositary shares will be entitled to delivery, at the office of the depositary to or upon his or her order, of the number of whole shares of the preferred stock and any money or other property represented by the depositary shares. If the depositary receipts delivered by the holder evidence a number of depositary shares in excess of the number of depositary shares representing the number of whole shares of preferred stock to be

withdrawn, the depositary will deliver to the holder at the same time a new depositary receipt evidencing the excess number of depositary shares. In no event will the depositary deliver fractional shares of preferred stock upon surrender of depositary receipts. Holders of preferred stock thus withdrawn may not thereafter deposit those shares under the deposit agreement or receive depositary receipts evidencing depositary shares therefor.

Redemption of Depositary Shares

Whenever we redeem shares of preferred stock held by the depositary, the depositary will redeem as of the same redemption date the number of depositary shares representing shares of the preferred stock so redeemed, so long as we have paid in full to the depositary the redemption price of the preferred stock to be redeemed plus an amount equal to any accumulated and unpaid dividends on the preferred stock to the date fixed for redemption. The redemption price per depositary share will be equal to the redemption price and any other amounts per share payable on the preferred stock multiplied by the fraction of a share of preferred stock represented by one depositary share. If less than all the depositary shares are to be redeemed, the depositary shares to be redeemed will be selected by lot or pro rata or by any other equitable method as may be determined by the depositary.

After the date fixed for redemption, depositary shares called for redemption will no longer be deemed to be outstanding and all rights of the holders of depositary shares will cease, except the right to receive the monies payable upon redemption and any money or other property to which the holders of the depositary shares were entitled upon redemption upon surrender to the depositary of the depositary receipts evidencing the depositary shares.

Voting the Preferred Stock

Upon receipt of notice of any meeting at which the holders of the preferred stock are entitled to vote, the depositary will mail the information contained in the notice of meeting to the record holders of the depositary receipts relating to that preferred stock. The record date for the depositary receipts relating to the preferred stock will be the same date as the record date for the preferred stock. Each record holder of the depositary shares on the record date will be entitled to instruct the depositary as to the exercise of the voting rights pertaining to the number of shares of preferred stock represented by that holder's depositary shares. The depositary will endeavor, insofar as practicable, to vote the number of shares of preferred stock represented by the depositary shares in accordance with those instructions, and we will agree to take all action that may be deemed necessary by the depositary in order to enable the depositary to do so. The depositary will not vote any shares of preferred stock except to the extent it receives specific instructions from the holders of depositary shares representing that number of shares of preferred stock.

Charges of Depositary

We will pay all transfer and other taxes and governmental charges arising solely from the existence of the depositary arrangements. We will pay charges of the depositary in connection with the initial deposit of the preferred stock and any redemption of the preferred stock. Holders of depositary receipts will pay transfer, income and other taxes and governmental charges and such other charges (including those in connection with the receipt and distribution of dividends, the sale or exercise of rights, the withdrawal of the preferred stock and the transferring, splitting or grouping of depositary receipts) as are expressly provided in the deposit agreement to be for their accounts. If these charges have not been paid by the holders of depositary receipts, the depositary may refuse to transfer depositary shares, withhold dividends and distributions and sell the depositary shares evidenced by the depositary receipt.

Amendment and Termination of the Deposit Agreement

The form of depositary receipt evidencing the depositary shares and any provision of the deposit agreement may be amended by agreement between us and the depositary. However, any amendment that materially and adversely alters the rights of the holders of depositary shares, other than fee changes, will not be effective unless the amendment has been approved by the holders of a majority of the outstanding depositary shares. The deposit agreement may be terminated by the depositary or us only if:

- all outstanding depositary shares have been redeemed; or
- there has been a final distribution of the preferred stock in connection with our dissolution and such distribution has been made to all the holders of depositary shares.

Resignation and Removal of Depositary

The depositary may resign at any time by delivering to us notice of its election to do so, and we may remove the depositary at any time. Any resignation or removal of the depositary will take effect upon our appointment of a successor depositary and its acceptance of such appointment. The successor depositary must be appointed within 60 days after delivery of the notice of resignation or removal and must be a bank or trust company having its principal office in the United States and having the requisite combined capital and surplus as set forth in the applicable agreement.

Notices

The depositary will forward to holders of depositary receipts all notices, reports and other communications, including proxy solicitation materials received from us, that are delivered to the depositary and that we are required to furnish to the holders of the preferred stock. In addition, the depositary will make available for inspection by holders of depositary receipts at the principal office of the depositary, and at such other places as it may from time to time deem advisable, any reports and communications we deliver to the depositary as the holder of preferred stock.

Limitation of Liability

Neither we nor the depositary will be liable if either is prevented or delayed by law or any circumstance beyond its control in performing its obligations. Our obligations and those of the depositary will be limited to performance in good faith of our and their duties thereunder. We and the depositary will not be obligated to prosecute or defend any legal proceeding in respect of any depositary shares or preferred stock unless satisfactory indemnity is furnished. We and the depositary may rely upon written advice of counsel or accountants, on information provided by persons presenting preferred stock for deposit, holders of depositary receipts or other persons believed to be competent to give such information and on documents believed to be genuine and to have been signed or presented by the proper party or parties.

DESCRIPTION OF PURCHASE CONTRACTS AND PURCHASE UNITS

We may issue purchase contracts, including contracts obligating holders to purchase from or sell to us, and obligating us to sell to or purchase from the holders, a specified number of shares of our common stock, preferred stock or depositary shares at a future date or dates, which we refer to in this prospectus as purchase contracts. The price per share of common stock, preferred stock or depositary shares and the number of shares of each may be fixed at the time the purchase contracts are issued or may be determined by reference to a specific formula set forth in the purchase contracts. The purchase contracts may be issued separately or as part of units, often known as purchase units, consisting of one or more purchase contracts and beneficial interests in debt securities or any other securities described in the applicable prospectus supplement or any combination of the foregoing, securing the holders' obligations to purchase the common stock, preferred stock or depositary shares under the purchase contracts.

The purchase contracts may require us to make periodic payments to the holders of the purchase units or vice versa, and these payments may be unsecured or prefunded on some basis. The purchase contracts may require holders to secure their obligations under those contracts in a specified manner, including pledging their interest in another purchase contract.

The applicable prospectus supplement will describe the terms of the purchase contracts and purchase units, including, if applicable, collateral or depositary arrangements.

DESCRIPTION OF WARRANTS

We may issue warrants to purchase debt securities, common stock, preferred stock or depositary shares. We may offer warrants separately or together with one or more additional warrants, debt securities, common stock, preferred stock or depositary shares, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

- the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants are to be sold separately or with other securities as parts of units;
- whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- the designation and terms of any equity securities purchasable upon exercise of the warrants;
- the designation, aggregate principal amount, currency and terms of any debt securities that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the debt securities, common stock, preferred stock or depositary shares with which the warrants are issued and, the number of warrants issued with each security;
- if applicable, the date from and after which any warrants issued as part of a unit and the related debt securities, common stock, preferred stock or depositary shares will be separately transferable;
- the number of shares of common stock, the number of shares of preferred stock or the number of depositary shares purchasable upon exercise of a warrant and the price at which those shares may be purchased;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the antidilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;
- any redemption or call provisions; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

FORMS OF SECURITIES

Each debt security, depositary share, purchase contract, purchase unit and warrant will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless otherwise provided in the applicable prospectus supplement, certificated securities in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depositary or its nominee as the owner of the debt securities, depositary shares, purchase contracts, purchase units or warrants represented by these global securities. The depositary maintains a computerized system that will reflect each investor's beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

Registered Global Securities

We may issue the registered debt securities, depositary shares, purchase contracts, purchase units and warrants in the form of one or more fully registered global securities that will be deposited with a depositary or its nominee identified in the applicable prospectus supplement and registered in the name of that depositary or nominee. In those cases, one or more registered global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal or face amount of the securities to be represented by registered global securities. Unless and until it is exchanged in whole for securities in definitive registered form, a registered global security may not be transferred except as a whole by and among the depositary for the registered global security, the nominees of the depositary or any successors of the depositary or those nominees.

If not described below, any specific terms of the depositary arrangement with respect to any securities to be represented by a registered global security will be described in the prospectus supplement relating to those securities. We anticipate that the following provisions will apply to all depositary arrangements.

Ownership of beneficial interests in a registered global security will be limited to persons, called participants, that have accounts with the depositary or persons that may hold interests through participants. Upon the issuance of a registered global security, the depositary will credit, on its book-entry registration and transfer system, the participants' accounts with the respective principal or face amounts of the securities beneficially owned by the participants. Any dealers, underwriters or agents participating in the distribution of the securities will designate the accounts to be credited. Ownership of beneficial interests in a registered global security will be shown on, and the transfer of ownership interests will be effected only through, records maintained by the depositary, with respect to interests of participants, and on the records of participants, with respect to interests of persons holding through participants. The laws of some states may require that some purchasers of securities take physical delivery of these securities in definitive form. These laws may impair your ability to own, transfer or pledge beneficial interests in registered global securities.

So long as the depositary, or its nominee, is the registered owner of a registered global security, that depositary or its nominee, as the case may be, will be considered the sole owner or holder of the securities represented by the registered global security for all purposes under the applicable indenture, deposit agreement, purchase contract, warrant agreement or purchase unit agreement. Except as described below, owners of beneficial interests in a registered global security will not be entitled to have the securities represented by the registered global security registered in their names, will not receive or be entitled to receive physical delivery of the securities in definitive form and will not be considered the owners or holders of the securities under the applicable indenture, deposit agreement,

purchase contract, purchase unit agreement or warrant agreement. Accordingly, each person owning a beneficial interest in a registered global security must rely on the procedures of the depository for that registered global security and, if that person is not a participant, on the procedures of the participant through which the person owns its interest, to exercise any rights of a holder under the applicable indenture, deposit agreement, purchase contract, purchase unit agreement or warrant agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a registered global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture, deposit agreement, purchase contract, purchase unit agreement or warrant agreement, the depository for the registered global security would authorize the participants holding the relevant beneficial interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to depository shares, warrants, purchase agreements or purchase units, represented by a registered global security registered in the name of a depository or its nominee will be made to the depository or its nominee, as the case may be, as the registered owner of the registered global security. None of us, the trustees, the warrant agents, the unit agents or any other agent of ours, agent of the trustees or agent of the warrant agents or unit agents will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the registered global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

We expect that the depository for any of the securities represented by a registered global security, upon receipt of any payment to holders of principal, premium, interest or other distribution of underlying securities or other property on that registered global security, will immediately credit participants' accounts in amounts proportionate to their respective beneficial interests in that registered global security as shown on the records of the depository. We also expect that payments by participants to owners of beneficial interests in a registered global security held through participants will be governed by standing customer instructions and customary practices, as is now the case with the securities held for the accounts of customers or registered in "street name," and will be the responsibility of those participants.

If the depository for any of the securities represented by a registered global security is at any time unwilling or unable to continue as depository or ceases to be a clearing agency registered under the Exchange Act, and a successor depository registered as a clearing agency under the Exchange Act is not appointed by us within 90 days, we will issue securities in definitive form in exchange for the registered global security that had been held by the depository. Any securities issued in definitive form in exchange for a registered global security will be registered in the name or names that the depository gives to the relevant trustee, warrant agent, unit agent or other relevant agent of ours or theirs. It is expected that the depository's instructions will be based upon directions received by the depository from participants with respect to ownership of beneficial interests in the registered global security that had been held by the depository.

PLAN OF DISTRIBUTION

We may sell securities:

- to or through underwriters, brokers or dealers;
- through agents;
- directly to one or more other purchasers in negotiated sales or competitively bid transactions;
- in "at the market" offerings, within the meaning of Rule 415(a)(4) of the Securities Act of 1933, as amended, or the Securities Act, to or through a market maker or into an existing trading market, on an exchange or otherwise;
- through a block trade in which the broker or dealer engaged to handle the block trade will attempt to sell the securities as agent, but may position and resell a portion of the block as principal to facilitate the transaction; or
- through a combination of any of the above methods of sale.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. We will, in the prospectus supplement relating to such offering, name any agent that could be viewed as an underwriter under the Securities Act and describe any commissions that we must pay. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

The distribution of the securities may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price;
- any discounts and commissions to be allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are utilized in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement or other agreement with them at

the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

If a dealer is utilized in the sale of the securities in respect of which the prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Certain agents, underwriters and dealers, and their associates and affiliates may be customers of, have borrowing relationships with, engage in other transactions with, or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallocate in connection with the offering, creating a short position for their own accounts. In addition, to cover overallocations or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in three business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than three scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the third business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than three scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

In compliance with the guidelines of the Financial Industry Regulatory Authority, or FINRA, the aggregate maximum discount, commission or agency fees or other items constituting underwriting compensation to be received by any FINRA member or independent broker-dealer will not exceed 8% of the proceeds from any offering pursuant to this prospectus and any applicable prospectus supplement.

LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Goodwin Procter LLP.

EXPERTS

The consolidated financial statements of Blueprint Medicines Corporation appearing in Blueprint Medicines Corporation's Annual Report on Form 10-K for the year ended December 31, 2016 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon, included therein and incorporated herein by reference. Such financial statements are incorporated herein by reference in reliance upon such report given on the authority of said firm as experts in auditing and accounting.

4,054,054 Shares

Blueprint Medicines Corporation

Common Stock



PROSPECTUS SUPPLEMENT

**Goldman Sachs & Co. LLC
Guggenheim Securities**

**Cowen
Wedbush PacGrow**

March 28, 2019
