

FIVE PRIME THERAPEUTICS INC

Form 424B5

January 25, 2018

Table of Contents

Filed Pursuant to Rule 424(b)(5)
Registration No. 333-214411

CALCULATION OF REGISTRATION FEE

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	5,897,435	\$19.50	\$114,999,983	\$14,318

- (1) Includes 769,230 shares that may be purchased by the underwriters upon exercise of the underwriters' option to purchase additional shares.
- (2) The filing fee is calculated and being paid pursuant to Rule 457(r) under the Securities Act of 1933 and relates to the Registration Statement on Form S-3 (File No. 333-214411) filed by the Registrant on November 3, 2016.

Table of Contents**PROSPECTUS SUPPLEMENT****(To Prospectus dated November 3, 2016)****5,128,205 Shares****Common Stock**

We are offering 5,128,205 shares of our common stock. Our common stock is listed on The Nasdaq Global Select Market under the symbol FPRX. On January 24, 2018, the last reported sales price of our common stock on The Nasdaq Global Select Market was \$20.14 per share.

Investing in our common stock involves risks. Please see Risk Factors beginning on page S-11 of this prospectus supplement for more information and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

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 supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	\$ 19.50	\$ 99,999,998
Underwriting discounts and commissions ⁽¹⁾	\$ 1.17	\$ 6,000,000
Proceeds to us, before expenses	\$ 18.33	\$ 93,999,998

(1) See Underwriting for additional disclosure regarding underwriting discounts and commissions and other estimated offering expenses.

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to an additional 769,230 shares of our common stock on the same terms as set forth above.

Delivery of the shares of common stock in this offering is expected to occur on or about January 29, 2018.

Goldman Sachs & Co. LLC

**J.P. Morgan
Wells Fargo Securities**

Leerink Partners

The date of this prospectus supplement is January 24, 2018.

Table of Contents

TABLE OF CONTENTS

Prospectus Supplement

	Page
<u>About this Prospectus Supplement</u>	S-1
<u>Prospectus Summary</u>	S-2
<u>The Offering</u>	S-9
<u>Risk Factors</u>	S-11
<u>Special Note Regarding Forward-Looking Statements</u>	S-13
<u>Use of Proceeds</u>	S-15
<u>Dividend Policy</u>	S-16
<u>Dilution</u>	S-17
<u>Material U.S. Federal Income Tax Consequences to Non-U.S. Holders</u>	S-18
<u>Underwriting</u>	S-22
<u>Legal Matters</u>	S-29
<u>Experts</u>	S-29
<u>Where You Can Find More Information</u>	S-29
<u>Incorporation of Certain Information by Reference</u>	S-30

Prospectus

	Page
<u>About this Prospectus</u>	i
<u>Prospectus Summary</u>	1
<u>Risk Factors</u>	2
<u>Special Note Regarding Forward-Looking Statements</u>	3
<u>Use of Proceeds</u>	5
<u>Description of Common Stock</u>	6
<u>Plan of Distribution</u>	10
<u>Legal Matters</u>	12
<u>Experts</u>	12
<u>Where You Can Find More Information</u>	12
<u>Incorporation of Certain Information by Reference</u>	12

Table of Contents

ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. This prospectus supplement describes the specific terms of this offering and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The accompanying prospectus gives more general information, some of which may not apply to this offering. If there is a difference between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring collectively to this prospectus supplement and the accompanying prospectus.

We have not, and underwriters have not, authorized anyone else to provide you with any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference herein and therein and any information contained in any free writing prospectus we have authorized for use in connection with this offering. We have not, and the underwriters have not, authorized anyone else to provide you with different information. We take, and the underwriters take, no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus supplement, the accompanying prospectus, the information in the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any authorized free writing prospectus is accurate only as of the date of those respective documents, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of shares of our common stock. Our business, financial condition, results of operations and prospects may have changed since those dates. It is important for you to read and consider all information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus in making your investment decision. You should read this prospectus supplement and the accompanying prospectus, as well as the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, and any authorized free writing prospectus. You should also read and consider the information in the documents we have referred you to in the sections of this prospectus supplement titled *Where You Can Find More Information* and *Incorporation of Certain Information by Reference*.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus supplement to Five Prime, the company, we, us, our and similar references refer to Five Prime Therapeutics, Inc. The Five Prime logo is our registered trademark. This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectuses we have authorized for use in connection with this offering, contains registered marks, trademarks and trade names of other companies, which are the property of their respective owners.

Table of Contents

PROSPECTUS SUMMARY

The following summary highlights selected information about us, this offering, and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents we incorporate by reference. Because this is only a summary, you should read the rest of this prospectus supplement, the accompanying prospectus, and our financial statements and related notes and the other information we incorporate by reference before you invest in our common stock. We encourage you to read this entire prospectus supplement and the accompanying prospectus and the information incorporated by reference carefully, especially the risks described under the section titled Risk Factors and in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which is incorporated herein by reference.

Our Company

We are a clinical-stage biotechnology company focused on discovering and developing innovative protein therapeutics to improve the lives of patients with serious diseases. Each of our product candidates has an innovative mechanism of action and addresses patient populations for which better therapies are needed. We have an emphasis in immuno-oncology, an area in which we have clinical, preclinical and discovery programs and product and discovery collaborations. In addition, we plan to use companion diagnostics where appropriate to allow us to select patients most likely to benefit from treatment with our product candidates. Our most advanced product candidates are identified below.

Cabiralizumab (FPA008) is an antibody that inhibits colony stimulating factor-1, or CSF1, receptor, or CSF1R, that we are studying in clinical trials as a monotherapy in tenosynovial giant cell tumor, also known as diffuse pigmented villonodular synovitis, or PVNS, and in multiple cancers in combination with Bristol-Myers Squibb Company's, or BMS, PD-1 immune checkpoint inhibitor, *Opdivo*® (nivolumab). In October 2015, we entered into a license and collaboration agreement, or the cabiralizumab collaboration agreement, with BMS, pursuant to which we granted BMS an exclusive worldwide license for the development and commercialization of cabiralizumab.

Bemarituzumab (FPA144) is an antibody that inhibits fibroblast growth factor receptor 2b, or FGFR2b, that we are initially developing to treat patients with gastric (stomach) or gastroesophageal junction, or GEJ, cancer and bladder cancer. In December 2017, we entered into a license and collaboration agreement, or the bemarituzumab collaboration agreement, with Zai Lab (Shanghai) Co., Ltd., or Zai Lab, pursuant to which we granted Zai Lab an exclusive license for the development and commercialization of bemarituzumab in China, Hong Kong, Macau and Taiwan.

FPA150 is a CD8 T cell checkpoint inhibitor antibody that targets B7-H4 that we are initially developing as a monotherapy in multiple cancers. We plan to begin a Phase 1 clinical trial for FPA150 in the first half of 2018.

We have a differentiated target discovery platform and extensive libraries of extracellular soluble proteins that we believe encompass substantially all of the body's medically important targets for protein therapeutics. We have identified approximately 700 of these proteins, which we refer to as the immunome, that we believe modulate immune cell interactions and may be important in understanding and treating cancer in patients using immuno-oncology therapeutics. Our target discovery platform and capabilities position us well to explore pathways in cancer and

inflammation and their intersection in immuno-oncology, an area of oncology with significant therapeutic potential and the focus of our research activities. We are applying our biologics discovery platform, including cell-based screening, immunome-by-immunome biophysical interaction screening, in vivo screening, receptor-ligand matching technologies and bioinformatics, in our immuno-oncology research program. We have identified several targets that we believe could be useful in immuno-oncology that we are actively validating, and we are also conducting research to discover additional targets. We generate and preclinically test

S-2

Table of Contents

therapeutic proteins, including antibodies and fusion proteins containing or directed to the targets we identify. We plan to continue to advance selected therapeutic candidates into clinical development.

We have no products approved for commercial sale and have not generated any revenue from product sales to date. We continue to incur significant research and development and other expenses related to our ongoing operations. We expect that our expenses will increase as we advance our product candidates into later stages of clinical development and increase the number of product candidates in clinical development. We have incurred losses in each period since our inception in 2002, with the exception of the fiscal year ended December 31, 2015, due primarily to the \$350.0 million upfront payment we received from BMS under our cabiralizumab collaboration agreement, and the fiscal year ended December 31, 2011, due primarily to the \$50.0 million upfront payment we received from GlaxoSmithKline from our license and collaboration agreement for FP-1039, our FGFR1-Fc fusion protein. For the nine months ended September 30, 2017 and 2016, we reported a net loss of \$121.0 million and \$45.6 million, respectively.

Recent Events

Cabiralizumab

In November 2017, we completed enrollment in the Phase 1b portion of our Phase 1a/1b clinical trial to evaluate the safety, tolerability and preliminary efficacy of combining cabiralizumab with *Opdivo* as a potential treatment for a variety of cancers.

In November 2017, we presented preliminary safety, tolerability and efficacy data from patients from the Phase 1a/1b clinical trial at the Society for Immunotherapy of Cancer 32nd Annual Meeting, or the SITC presentation. As of the August 1, 2017 data cutoff for the SITC presentation, we had tested cabiralizumab as monotherapy in advanced solid tumors at escalating doses of cabiralizumab in 24 patients, in combination with *Opdivo* in advanced solid tumors at escalating doses of cabiralizumab in 10 patients, and in combination with *Opdivo* in advanced solid tumors in disease-specific cohorts at a dose of 4 mg/kg of cabiralizumab every two weeks in 195 patients. We observed a tolerable safety profile of cabiralizumab monotherapy and of cabiralizumab in combination with *Opdivo*. The most common treatment-related laboratory abnormalities were elevations in creatine kinase and serum liver enzymes without an associated elevation in bilirubin levels or other clinical sequelae. These treatment-related adverse abnormalities are believed to be secondary to cabiralizumab's depletion of Kupffer cells and have been observed with other CSF1R-targeting agents. The most common treatment-related adverse events were: periorbital edema (20.8%), fatigue (29.2%), nausea (12.5%) and pruritus (8.3%). Grade 5 treatment-related adverse events in the trial occurred in three (1.3%) patients treated with a combination of cabiralizumab and *Opdivo*. The Grade 5 events were pneumonitis in a patient with thyroid cancer and respiratory distress and acute respiratory distress in two patients with lung cancer.

Among the other data, we observed preliminary evidence of a durable clinical benefit of the combination therapy in the cohort of patients with advanced pancreatic cancer. Based on radiographic assessments of anti-tumor activity in the 31 second- or later-line patients who had advanced pancreatic cancer, we observed, as of the August 1, 2017 data cutoff date:

five patients with durable clinical benefit (16%);

four confirmed objective responses (13%); and

disease control for at least five to over nine months.

All four confirmed objective responses were in patients with microsatellite stable tumors who had received an average of three prior therapies. In addition, the responses were accompanied by steep declines in levels of the pancreatic tumor marker CA-19-9 over the baseline.

S-3

Table of Contents

The data suggest that a combination therapy of cabiralizumab with *Opdivo* may benefit patients with pancreatic cancer, including those with microsatellite stable tumors, and support further study of cabiralizumab in combination with *Opdivo* in pancreatic cancer.

Based on the clinical data we observed in the cohort of patients with pancreatic cancer in the Phase 1a/1b trial, we are in the process of enrolling approximately 30 patients with second- or later-line pancreatic cancer in the Phase 1a portion of our Phase 1a/1b clinical trial to further evaluate the combination of cabiralizumab and *Opdivo* in this patient population. We are collecting pre- and on-treatment tumor biopsy samples from these patients, and are conducting comprehensive biomarker analyses to evaluate potential biomarker signatures that may predict responsiveness to this therapeutic combination and to assess changes that occur in the tumor microenvironment following treatment.

BMS is currently recruiting patients for a randomized, multi-arm Phase 2 clinical trial to determine the efficacy of cabiralizumab in combination with *Opdivo*, with and without chemotherapy, as a treatment for patients with second-line pancreatic cancer (NCT03336216). BMS plans to enroll approximately 160 patients with pancreatic cancer in the study, who will be randomized to one of four study arms based on the patient's prior therapy. The dosing of the first patient in the trial by BMS will trigger a \$25 million milestone payable to us under the license and collaboration agreement between the companies established in 2015.

Bemarituzumab (FPA144)***Phase 1 Clinical Trial of Bemarituzumab (FPA144) in Gastric and GEJ Cancer***

We are conducting a Phase 1 clinical trial of bemarituzumab (FPA144) to evaluate the safety, pharmacokinetics, or PK, and efficacy of bemarituzumab as a monotherapy in patients with metastatic gastric and GEJ cancer and bladder cancer whose tumors overexpress the FGFR2b protein. In June 2017, we presented updated safety and efficacy data from the Phase 1 clinical trial in a clinical poster at the 2017 ASCO Annual Meeting, or the ASCO presentation. As of the March 20, 2017 data cut-off date for the ASCO presentation, we had tested bemarituzumab in advanced solid tumors at doses of up to 15 mg/kg given as monotherapy every two weeks, including in patients with gastric or GEJ cancer and one patient with bladder cancer. We did not observe any dose-limiting toxicities or a maximum-tolerated dose. In addition, unlike small molecule FGF receptor kinase inhibitors, which block signaling through a broad number of FGF receptors and can lead to hyperphosphatemia, we did not observe any treatment-related hyperphosphatemia in patients treated with bemarituzumab. All treatment-related adverse events were Grades 1, 2 or 3. All treatment-related ocular adverse events were Grades 1 or 2, and no retinal toxicity was reported.

With respect to the patients with gastric or GEJ cancer, we observed preliminary anti-tumor activity with bemarituzumab monotherapy in late-line patients who had a median of three prior therapies and whose tumors overexpress the FGFR2b protein. Based on radiographic assessments by RECIST 1.1 of anti-tumor activity in the 21 patients who had high FGFR2b+ overexpressing gastric or GEJ cancer, we observed, as of the March 20, 2017 data cut-off date:

four confirmed partial responses (one each at the 6 mg/kg and 10 mg/kg dose levels and two at the 15 mg/kg dose levels); one unconfirmed partial response (at the 15 mg/kg dose level);

an objective response rate, or ORR, of 19.0%;

a median duration of response of 15.4 weeks; and

a disease control rate, or DCR, at 6 weeks of 57.1%.

In September 2017, we closed enrollment in the expansion cohorts of metastatic gastric and GEJ cancer in our Phase 1 clinical trial to focus efforts on preparing for our global Phase 1/3 registrational trial of

S-4

Table of Contents

bemarituzumab in combination with 5-fluorouracil (5-FU), leucovorin, and oxaliplatin, or mFOLFOX6, as front-line treatment of patients with gastric and GEJ cancer that overexpresses FGFR2b, or the FIGHT trial. We continue to enroll patients in the bladder cancer expansion cohort in our Phase 1 trial.

Phase 1/3 FIGHT Clinical Trial

We designed our initial Phase 1 clinical trial testing beemarituzumab as monotherapy to evaluate the safety and tolerability of beemarituzumab as well as to gain early evidence of effectiveness, including by evaluating ORR, DCR and duration of response of patients with gastric or GEJ cancer that overexpresses FGFR2b. We have generated ORR, DCR and duration of response and safety data in our initial Phase 1 clinical trial that we believe support the evaluation of beemarituzumab in a registrational trial. Because patients with gastric or GEJ cancer that overexpresses FGFR2b have a worse prognosis as compared to those patients that do not overexpress FGFR2b, we believe that patients with FGFR2b-overexpressing disease progress more rapidly and that such patients are less likely to survive and become third- or even second-line patients. As a result, we believe testing beemarituzumab as a front-line treatment would increase the pool of patients that would be eligible to enroll in the trial and would result in faster enrollment and completion of a registrational trial than had we decided to test beemarituzumab as a second- or third-line treatment. In addition, because of the heterogeneity of advanced gastric and GEJ cancer, and because our preclinical data show additive efficacy against FGFR2b-overexpressing gastric cancer when adding beemarituzumab to chemotherapy, we believe that testing beemarituzumab in combination with chemotherapy may increase the extent and duration of response as compared to treatment with beemarituzumab alone. Moreover, we believe that beemarituzumab's safety profile allows for the combination of beemarituzumab with chemotherapy while maintaining an acceptable safety profile. Based on the foregoing, we designed the FIGHT trial to test beemarituzumab in combination with mFOLFOX6 as front-line treatment of patients with gastric or GEJ cancer that overexpresses FGFR2b.

Because we have not yet clinically tested beemarituzumab in combination with mFOLFOX6, we included a Phase 1 safety lead-in for the FIGHT trial. During this Phase 1 safety lead-in portion of the FIGHT trial, we will evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of beemarituzumab in combination with mFOLFOX6 in patients with any type of gastrointestinal cancer to identify a recommended dose of beemarituzumab to use in the Phase 3 portion of the trial. In December 2017, we initiated dosing in the Phase 1 safety lead-in portion of the FIGHT trial. We expect to initiate the Phase 3 portion of the trial in mid-2018.

Exclusive License Agreement with Zai Lab

In December 2017, we entered into the beemarituzumab collaboration agreement with Zai Lab, pursuant to which we granted Zai Lab an exclusive license to develop and commercialize beemarituzumab, and all fragments, conjugates, derivatives and modifications thereof, or the licensed antibody, in China, Hong Kong, Macau, and Taiwan, each a region, and collectively, the territory.

Under the terms of the beemarituzumab collaboration agreement, Zai Lab will be responsible, at its expense, for (i) developing and commercializing products containing the licensed antibody, each, a licensed product, under a territory development plan and (ii) performing certain development activities to support our global development and registration of licensed products, including the Phase 3 portion of the FIGHT trial, in the territory, under a global development plan.

Pursuant to the beemarituzumab collaboration agreement, we earned a \$5 million upfront payment from Zai Lab in December 2017. Additionally, with respect to each licensed product, we are eligible to receive up to \$39 million in specified development and regulatory milestone payments.

Zai Lab will also be obligated to pay us a royalty, on a licensed product-by-licensed product and region-by-region basis, in the high teens or low twenties, depending on the number of patients Zai Lab enrolls in

S-5

Table of Contents

the FIGHT trial, subject to reduction in certain circumstances, on net sales of each licensed product in the territory until the latest of (i) the 11th anniversary of the first commercial sale of such licensed product in such region, (ii) the expiration of certain patents covering such licensed product in such region, and (iii) the date on which any applicable regulatory, pediatric, orphan drug or data exclusivity with respect to such licensed product expires in such region. We cannot determine the date on which Zai Lab's potential royalty payment obligations to us would expire because Zai Lab has not yet developed any licensed products under the beemarituzumab collaboration agreement, and we therefore cannot at this time identify the date of the first commercial sale or any related patents covering or regulatory exclusivity periods with respect to such licensed product.

Under the agreement, provided that Zai Lab enrolls and treats a specified number of patients in the FIGHT trial in China, Zai Lab is eligible to receive a low single-digit percentage royalty, on a licensed product-by-licensed product basis on net sales of a licensed product outside the territory until the 10th anniversary of the first commercial sale of each such licensed product outside the territory.

Unless earlier terminated by either party, the beemarituzumab collaboration agreement will expire on a licensed product-by-licensed product and region-by-region basis upon the expiration of Zai Lab's payment obligations with respect to each licensed product under the agreement. Zai Lab may terminate the agreement in its entirety at any time with advance written notice. Either party may terminate the agreement in its entirety with written notice for the other party's material breach if such party fails to cure the breach. We may terminate the agreement in its entirety with written notice for Zai Lab's material breach of its diligence obligations with respect to development and obtaining marketing approval, and may terminate the agreement on a region-by-region basis for Zai Lab's breach of its diligence obligations with respect to timely commercialization of a licensed product in a region following marketing approval. We may terminate the agreement in its entirety if Zai Lab or its affiliates or sublicensees commences a legal action challenging the validity, enforceability or scope of any of our patents in the territory. Either party also may terminate the agreement in its entirety upon certain insolvency events involving the other party.

FPA150

In December 2017, we filed an IND to initiate a Phase 1a/1b clinical trial to evaluate the safety, tolerability and preliminary efficacy of FPA150 monotherapy as a potential therapy in patients with a variety of cancers. In January 2018, we received clearance from the FDA to proceed with the clinical development of FPA150.

BMS Discovery Collaboration Agreement

In December 2017, we earned a \$5 million milestone payment under our March 2014 discovery collaboration agreement with BMS in connection with BMS's filing of an IND for its fully-human monoclonal antibody targeting TIM-3 (T-cell immunoglobulin and mucin domain-3), an immune checkpoint receptor that is known to limit the duration and magnitude of T-cell responses. This antibody is BMS's first clinical candidate arising from the collaboration.

In addition, BMS exercised its option to extend the research term of the collaboration to March 2019. BMS will provide us with funding for the additional research we will conduct during the extended term. This is the second extension to the original collaboration term under the agreement.

Table of Contents**Clinical Pipeline**

The following table shows the stage of development of our most advanced product candidates:

* Partnered with BMS see Part I Item 1. Collaborations of our most recent Annual Report on Form 10-K for a description of the commercial arrangement with BMS.

** Partnered with Zai Lab see our Current Report on Form 8-K filed with the SEC on December 19, 2017 for a description of the beemarituzumab collaboration agreement with Zai Lab.

Preliminary Financial Results

We are currently finalizing our financial results for the fiscal year ended December 31, 2017. While complete financial information and operating data are not available, based on information currently available, we estimate the following:

	As of December 31, 2017 (Unaudited)
Cash, cash equivalents and marketable securities	\$ 293 million
Common stock outstanding	29.0 million

These preliminary estimates have been prepared by, and are the responsibility of, our management. Our independent registered public accounting firm, Ernst & Young LLP, has not audited or reviewed, and does not express an opinion with respect to, these estimates. Actual results and financial data as of December 31, 2017 may differ from the above estimates due to the completion of our closing procedures with respect to the fiscal year ended December 31, 2017, final adjustments and other developments that may arise between now and the time the financial results for the fiscal year are finalized. We expect to complete our closing procedures with respect to the fiscal year ended December 31, 2017 after this offering is consummated. Accordingly, our consolidated financial statements as of and for the fiscal year ended December 31, 2017 will not be available until after this offering is completed.

Table of Contents

Our Corporate Information

We were incorporated under the laws of the State of Delaware in December 2001. Our principal executive office is located at 111 Oyster Point Boulevard, South San Francisco, California 94080, and our telephone number is (415) 365-5600. Our website address is www.fiveprime.com. Our website and the information contained on, or that can be accessed through, our website will not be deemed to be incorporated by reference in, and are not considered part of, this prospectus supplement or the accompanying prospectus. You should not rely on any such information in making your decision whether to purchase our common stock.

S-8

Table of Contents

THE OFFERING

Common stock to be offered by us	5,128,205 shares
Common stock to be outstanding immediately following this offering	34,010,695 shares (or 34,779,925 shares if the underwriters exercise their option to purchase additional shares in full).
Option to purchase additional shares from us	We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to an additional 769,230 shares of our common stock.

Use of proceeds

We expect to use the net proceeds from this offering, together with other available funds, (i) to advance and expand the clinical development of our bemarituzumab (FPA144) program, including to fund our portion of the Phase 1/3 FIGHT trial outside of greater China, (ii) to advance clinical development of our cabiralizumab (FPA008) program in PVNS, (iii) to fund additional research and pre-clinical development of cabiralizumab in immuno-oncology outside of pancreatic cancer and in combination with other candidates in our research and development pipeline, (iv) to advance our FPA150 and FPT155 programs into clinical development, (v) to fund additional research and pre-clinical development activities for our other immuno-oncology programs and (vi) for working capital and general corporate purposes. Although we may use a portion of the net proceeds from this offering for the licensing or acquisition of, or the development of, additional product candidates, technologies, compounds, other assets or complementary businesses, we have no current understandings, agreements or commitments to do so. See Use of Proceeds.

Risk factors

Investing in our common stock involves a high degree of risk. See Risk Factors and other information included in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.

Nasdaq Global Select Market symbol FPRX

The number of shares of common stock outstanding immediately following this offering set forth above is based on 28,882,490 shares of common stock outstanding as of September 30, 2017. This number excludes:

Edgar Filing: FIVE PRIME THERAPEUTICS INC - Form 424B5

3,858,321 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2017, under our existing equity incentive plans, at a weighted-average exercise price of \$29.55 per share;

1,461,211 shares of our common stock reserved as of September 30, 2017 for future issuance under our 2013 Omnibus Incentive Plan, or 2013 Plan, as well as any future increases in the number of shares of our common stock reserved for issuance under the 2013 Plan; and

S-9

Table of Contents

969,453 shares of our common stock reserved as of September 30, 2017 for future issuance under our 2013 Employee Stock Purchase Plan, or the ESPP, as well as any future increases in the number of shares of our common stock reserved for issuance under the ESPP.

Subsequent to September 30, 2017, and through the date of this prospectus supplement:

we reserved an additional 1,159,282 shares of common stock for future issuance under the 2013 Plan; and

we reserved an additional 289,821 shares of common stock for future issuance under the ESPP.

Unless otherwise indicated, all information in this prospectus supplement assumes:

no exercise of outstanding stock options; and

no exercise by the underwriters of their option to purchase additional shares.

Table of Contents**RISK FACTORS**

*An investment in our common stock involves a high degree of risk. You should carefully consider the following risk factors and the risk factors discussed under the section titled **Risk Factors** contained in our **Quarterly Report on Form 10-Q** for the quarter ended September 30, 2017, which are incorporated by reference into this prospectus supplement in their entirety, together with all of the other information contained in this prospectus supplement and the accompanying prospectus or incorporated by reference into this prospectus supplement and the accompanying prospectus. The risks and uncertainties described in these documents are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below or in our **Quarterly Report on Form 10-Q** for the quarter ended September 30, 2017 actually occur, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the value of our common stock to decline, and you may lose all or part of your investment.*

Risks Related to this Offering

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, and you will be relying on the judgment of our management regarding the application of these proceeds. You will not have the opportunity, as part of your investment decision, to assess whether we are using the proceeds appropriately. We expect to use the net proceeds from this offering, together with other available funds, (i) to advance and expand the clinical development of our bemarituzumab (FPA144) program, including to fund our portion of the Phase 1/3 FIGHT trial outside of greater China, (ii) to advance clinical development of our cabiralizumab (FPA008) program in PVNS, (iii) to fund additional research and pre-clinical development of cabiralizumab in immuno-oncology outside of pancreatic cancer and in combination with other candidates in our research and development pipeline, (iv) to advance our FPA150 and FPT155 programs into clinical development, (v) to fund additional research and pre-clinical development activities for our other immuno-oncology programs and (vi) for working capital and general corporate purposes. Although we may use a portion of the net proceeds from this offering for the licensing or acquisition of, or the development of, additional product candidates, technologies, compounds, other assets or complementary businesses, we have no current understandings, agreements or commitments to do so. However, our use of these net proceeds may differ substantially from our current plans and our management might not apply our net proceeds in ways that ultimately increase the value of your investment. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

If you purchase our common stock in this offering, you will experience immediate and substantial dilution in investment. You will experience further dilution if we issue additional equity securities in future fundraising transactions.

Since the public offering price per share of our common stock is substantially higher than the net tangible book value per share of our common stock, you will suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. As a result, investors purchasing shares of common stock in this offering will incur immediate dilution of approximately \$8.34 per share, based upon the public offering price of \$19.50 per share and our net tangible book value as of September 30, 2017, after giving effect to this offering. See the section titled **Dilution** below for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

Sales of a substantial amount of shares of our common stock in the public market, particularly sales by our directors, executive officers and significant stockholders, or the perception that these sales could occur, could cause the market price of our common stock to decline and may make it more difficult for you to sell your

S-11

Table of Contents

common stock at a time and price that you deem appropriate. In addition, we have a significant number of shares reserved for issuance in connection upon vesting or exercise of outstanding awards under our equity compensation plans. To the extent that these awards vest or are exercised, investors purchasing our common stock in this offering may experience further dilution. 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 or result in downward pressure on the price of our common stock.

Our executive officers and directors have entered into lock-up agreements with us under which we and they have agreed, subject to specific exceptions described in the section titled *Underwriting*, not to sell, directly or indirectly, any shares of common stock without the permission of the underwriters for a period of 90 days following the date of this prospectus supplement. We refer to such period as the lock-up period. When the lock-up period expires, we and our executive officers and directors will be able to sell our shares in the public market. In addition, the underwriters may, in their sole discretion, release all or some portion of the shares subject to lock-up agreements at any time and for any reason. Sales of a substantial number of such shares upon expiration of the lock-up, the perception that such sales may occur, or early release of these agreements, could cause our market price to fall or make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, and any free writing prospectus that we have authorized for use in connection with this offering contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, which we refer to as the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act, that involve substantial risks and uncertainties. In some cases you can identify these statements by forward-looking words such as believe, may, will, estimate, continue, anticipate, intend, project, plan, expect or similar expressions, or the negative or plural of these words or expressions. Discussions containing these forward-looking statements may be found, among other places, in Business, Risk Factors and Management's Discussion and Analysis of Financial Condition and Results of Operations incorporated by reference from our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q filed with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC. These statements involve risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. These forward-looking statements include, but are not limited to, statements concerning the following:

our planned uses for the net proceeds we expect to receive from this offering;

our estimates regarding our expenses, revenues, anticipated capital requirements and our needs for additional financing;

our potential receipt of future milestone payments or royalties, and the timing of such payments;

our or our partners' ability to timely advance drug candidates into and through clinical data readouts and successful completion of clinical trials;

the timing of the initiation, progress and results of preclinical studies and research and development programs;

our expectations regarding the potential safety, efficacy or clinical utility of our product candidates;

the implementation, timing and likelihood of success of our plans to develop companion diagnostics for our product candidates;

our ability to establish and maintain collaborations and necessary licenses;

the implementation of our business model and strategic plans for our business, product candidates and technology;

the scope of protection we establish and maintain for intellectual property rights covering our product candidates and technology;

the size of patient populations targeted by products we or our partners develop and market adoption of such products by physicians and patients;

the timing or likelihood of regulatory filings and approvals;

the ability to negotiate adequate reimbursement and pricing for our product candidates by third parties and government authorities;

developments relating to our competitors and our industry; and

our expectations regarding licensing, acquisitions and strategic operations.

In addition, you should refer to the Risk Factors section in any free writing prospectus we may authorize for use in connection with this offering for a discussion of other important factors, risks and uncertainties that

Table of Contents

may cause our actual results to differ materially from those expressed or implied by these forward-looking statements. Given these other important factors, risks and uncertainties, you should not place undue reliance on these forward-looking statements. Also, these forward-looking statements represent our estimates and assumptions only as of the date such forward-looking statements are made. You should carefully read this prospectus supplement and the accompanying prospectus, together with the information incorporated by reference herein and therein completely and with the understanding that our actual future results may be materially different from what we expect. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our business, results of operations and financial condition.

In addition, statements that we believe and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus supplement, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

You should rely only on information contained or incorporated by reference in this prospectus supplement, the accompanying prospectus, the registration statement of which this prospectus supplement is a part, including the exhibits that we have filed with the registration statement, and in any free writing prospectus we may authorize for use in connection with this offering. You should understand that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Except as required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. You should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. Before deciding to invest, you should carefully consider the risk factors discussed and incorporated by reference in this prospectus supplement and the accompanying prospectus or in any free writing prospectus that we may have authorized for use in connection with this offering.

Table of Contents

USE OF PROCEEDS

We expect to receive approximately \$93.5 million in net proceeds from the sale of 5,128,205 shares of common stock offered by us in this offering (approximately \$107.6 million if the underwriters exercise their option to purchase 769,230 additional shares in full) after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We expect to use the net proceeds from this offering, together with other available funds, (i) to advance and expand the clinical development of our bemarituzumab (FPA144) program, including to fund our portion of the Phase 1/3 FIGHT trial outside of greater China, (ii) to advance clinical development of cabiralizumab in PVNS, (iii) to fund additional research and pre-clinical development of cabiralizumab in immuno-oncology outside of pancreatic cancer and in combination with other candidates in our research and development pipeline, (iv) to advance our FPA150 and FPT155 programs into clinical development, (v) to fund additional research and pre-clinical development activities for our other immuno-oncology programs and (vi) for working capital and general corporate purposes.

The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures depend on numerous factors, including the progress of our preclinical development efforts, the ongoing status of and results from our clinical trials and other studies and any unforeseen cash needs. As a result, our management will have broad discretion in applying the net proceeds from this offering. Although we may use a portion of the net proceeds from this offering for the licensing or acquisition of, or the development of, additional product candidates, technologies, compounds, other assets or complementary businesses, we have no current understandings, agreements or commitments to do so. Pending their ultimate use, we intend to invest the net proceeds from this offering in interest-bearing, investment-grade securities.

Table of Contents

DIVIDEND POLICY

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

S-16

Table of Contents**DILUTION**

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the public offering price per share of our common stock and the as adjusted net tangible book value per share of our common stock immediately after this offering. Net tangible book value per share of our common stock is determined at any date by subtracting our total liabilities from the amount of our total tangible assets and dividing the difference by the number of shares of our common stock deemed to be outstanding at that date.

Our net tangible book value as of September 30, 2017 was approximately \$286.1 million, or \$9.91 per share, based on 28,882,490 shares of common stock outstanding as of September 30, 2017. After giving effect to the sale of 5,128,205 shares of common stock in this offering at the public offering price of \$19.50 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2017 would have been \$379.6 million, or \$11.16 per share. This amount represents an immediate increase in net tangible book value of \$1.25 per share of our common stock to existing stockholders and an immediate dilution in net tangible book value of \$8.34 per share of our common stock to new investors purchasing shares of common stock in this offering.

The following table illustrates this dilution on a per share basis to new investors:

Public offering price per share	\$ 19.50
Net tangible book value per share as of September 30, 2017	\$ 9.91
Increase in net tangible book value per share attributable to new investors	1.25
As adjusted net tangible book value per share after this offering	11.16
Dilution per share to new investors purchasing common stock in this offering	\$ 8.34

The information above assumes that the underwriters do not exercise their option to purchase additional shares. If the underwriters exercise their option in full at the public offering price of \$19.50, our as adjusted net tangible book value per share as of September 30, 2017 after giving effect to this offering would have been \$11.32 per share and the dilution in as adjusted net tangible book value per share to investors in this offering would have been \$8.18 per share.

The number of shares of common stock outstanding immediately following this offering is based on 28,882,490 shares of common stock outstanding as of September 30, 2017. This number excludes:

3,858,321 shares of our common stock issuable upon the exercise of stock options outstanding as of September 30, 2017, under our existing equity incentive plans, at a weighted-average exercise price of \$29.55 per share;

1,461,211 shares of our common stock reserved as of September 30, 2017 for future issuance under the 2013 Plan as well as any future increases in the number of shares of our common stock reserved for issuance under the 2013 Plan; and

969,453 shares of our common stock reserved as of September 30, 2017 for future issuance under the ESPP as well as any future increases in the number of shares of our common stock reserved for issuance under the ESPP.

Subsequent to September 30, 2017, and through the date of this prospectus supplement:

we reserved an additional 1,159,282 shares of common stock for future issuance under the 2013 Plan; and

we reserved an additional 289,821 shares of common stock for future issuance under the ESPP.

To the extent that any options are exercised, new options are issued under our equity incentive plans or we otherwise issue additional shares of common stock in the future at a price less than the public offering price, there may be further dilution to new investors purchasing common stock in this offering.

Table of Contents

MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following is a summary of certain material U.S. federal income tax considerations relating to the purchase, ownership and disposition of our common stock applicable to non-U.S. holders as defined below. This discussion is not a complete analysis of all of the potential U.S. federal income tax consequences relating thereto, nor does it address any tax consequences arising under any state, local or foreign tax laws, or any other U.S. federal tax laws. 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, possibly retroactively, 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 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. The term non-U.S. holder means a beneficial owner of our common stock that, for U.S. federal income tax purposes, is not an entity taxable as a partnership, or any of the following:

an individual who is a citizen or resident of the U.S.;

a corporation or other entity taxable as a corporation for U.S. federal income tax purposes created or organized in the U.S. or under the laws of the U.S., any state thereof, or the District of Columbia or otherwise treated as such for U.S. federal income tax purposes;

an estate, the income of which is subject to U.S. federal income taxation regardless of its source; or

a trust that (1) is subject to the primary supervision of a U.S. court and the control of one or more United States persons (as defined in Section 7701(a)(30) of the Code), each, a U.S. person, or (2) has a valid election in effect under applicable Treasury regulations to be treated as a U.S. person.

This summary is limited to non-U.S. holders who purchase shares of our common stock issued pursuant to this offering and who hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment). 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;

persons subject to the alternative minimum tax or the net investment income tax;

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;

controlled foreign corporations, passive foreign investment companies or corporations that accumulate earnings to avoid U.S. federal income tax;

persons that are partnerships or other pass-through entities or partners or members of such entities or entities that are disregarded for tax purposes;

certain former citizens or long-term residents of the U.S.; or

persons who hold our common stock as part of a hedge, straddle, constructive sale, or conversion transaction.

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

S-18

Table of Contents

STOCK ARISING UNDER THE FEDERAL ESTATE OR GIFT TAX RULES OR UNDER THE LAWS OF ANY STATE, LOCAL, FOREIGN OR OTHER TAXING JURISDICTION OR UNDER ANY APPLICABLE TAX TREATY.

Distributions on Common Stock

As described in the section titled **Dividend Policy**, we do not anticipate declaring or paying cash dividends to holders of our common stock in the foreseeable future. However, if we do make cash or other property distributions on our common stock, such distributions 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. Distributions in excess of our earnings and profits will constitute a return of capital that will first be applied against and reduce the non-U.S. holder's adjusted tax basis in our common stock, but not below zero. Any remaining excess will be treated as gain realized on the sale or other disposition of the common stock and will be treated as described under **Gain on Disposition of Common Stock** below.

Dividends paid to a non-U.S. holder that are not effectively connected with the non-U.S. holder's conduct of a trade or business in the U.S. will generally be subject to withholding of U.S. federal income tax at the rate of 30%, or if a tax treaty applies, a lower rate specified by the treaty. Non-U.S. holders should consult their tax advisors regarding their entitlement to benefits under a relevant income tax treaty.

Dividends that are effectively connected with a non-U.S. holder's conduct of a trade or business in the U.S. and, if an income tax treaty applies, are attributable to a permanent establishment in the U.S., are generally exempt from withholding and will be taxed on a net income basis at the same graduated U.S. federal income tax rates applicable to a U.S. person. In such cases, we will not have to withhold U.S. federal income tax if the non-U.S. holder complies with applicable certification requirements. In addition, if the non-U.S. holder is a corporation, a branch profits tax equal to 30% (or lower applicable treaty rate) may be imposed on a portion of its effectively connected earnings and profits for the taxable year. Non-U.S. holders should consult their tax advisors regarding any applicable tax treaties that may provide for different rules.

To claim the benefit of a tax treaty or an exemption from withholding because the dividends are effectively connected with the conduct of a trade or business in the U.S., a non-U.S. holder must either (a) provide a properly executed applicable IRS Form W-8 before the payment of dividends or (b) if our common stock is held through certain foreign intermediaries, satisfy the relevant certification requirements of applicable U.S. Treasury regulations. These forms may need to be periodically updated. Non-U.S. holders may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the IRS.

For additional withholding rules that may apply to dividends paid to certain foreign entities, see the discussions below under the headings **Information Reporting and Backup Withholding** and **Foreign Account Tax Compliance Act**.

Gain on Disposition of Common Stock

Subject to the discussions below regarding the Foreign Account Tax Compliance Act and Information Reporting and Backup Withholding, a non-U.S. holder generally will not be subject to U.S. federal income tax or any withholding thereof with respect to gain recognized on a sale or other disposition of our common stock unless one of the following applies:

the gain is effectively connected with the non-U.S. holder's conduct of a trade or business in the U.S. and, if an income tax treaty applies, is attributable to a permanent establishment maintained by the non-U.S. holder in the U.S.; in these cases, the non-U.S. holder will generally be taxed on its net gain derived from the disposition at the same graduated U.S. federal income tax rates applicable to a U.S. person and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above may also apply;

S-19

Table of Contents

the non-U.S. holder is a non-resident alien individual who is present in the U.S. for 183 days or more in the taxable year of the disposition and meets certain other requirements; in this case, the non-U.S. holder will be subject to U.S. federal income tax at a rate of 30% (or a reduced rate under an applicable treaty) on the amount by which capital gains (including gain recognized on a sale or other disposition of our common stock) allocable to U.S. sources exceed capital losses allocable to U.S. sources (provided that the non-U.S. holder has timely filed U.S. income tax returns with respect to such losses); or

our common stock constitutes a United States real property interest by reason of our status as a United States real property holding corporation, or USRPHC, for U.S. federal income tax purposes at any time during the shorter of the 5-year period ending on the date you dispose of our common stock or the period you held our common stock. The determination of whether we are a USRPHC depends on the fair market value of our U.S. real property interests relative to the fair market value of our other business assets. We believe that we currently are not and do not anticipate becoming a USRPHC. Even if we are or were to become a USRPHC, gain arising from the sale or other taxable disposition by a non-U.S. Holder of our common stock will not be subject to U.S. federal income tax if our common stock is regularly traded, as defined by applicable Treasury regulations, on an established securities market, and such non-U.S. Holder owned, actually and constructively, 5% or less of our common stock throughout the shorter of the five-year period ending on the date of the sale or other taxable disposition or the non-U.S. Holder's holding period. There can be no assurance that our common stock will in fact be regularly traded on an established securities market through the relevant periods.

Information Reporting and Backup Withholding

We must report annually to the IRS the amount of dividends or other distributions we pay to you on your shares of common stock and the amount of tax we withhold on these distributions regardless of whether withholding is required. The IRS may make copies of the information returns reporting those distributions and amounts withheld available to the tax authorities in the country in which you reside pursuant to the provisions of an applicable income tax treaty or exchange of information treaty. Backup withholding tax may also apply to payments made to a non-U.S. holder on or with respect to our common stock, unless the non-U.S. holder certifies as to its status as a non-U.S. holder, such as by furnishing a properly executed applicable IRS Form W-8, under penalties of perjury or otherwise establishes an exemption, and certain other conditions are satisfied. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder is a U.S. person that is not an exempt recipient.

Information reporting and backup withholding generally are not required with respect to the amount of any proceeds from the sale of your shares of common stock outside the U.S. through a foreign office of a foreign broker that does not have certain specified connections to the U.S. However, if you sell your shares of common stock through a U.S. broker or the U.S. office of a foreign broker, the broker will be required to report to the IRS the amount of proceeds paid to you and also perform backup withholding on that amount unless you provide appropriate certification to the broker of your status as a non-U.S. holder, such as by furnishing a properly executed applicable IRS Form W-8, or you otherwise establish an exemption. Information reporting will also apply if you sell your shares of common stock through a foreign broker deriving more than a specified percentage of its income from U.S. sources or having certain other connections to the U.S., unless such broker has documenting evidence in its records that you are a non-U.S. holder and certain other conditions are met or you otherwise establish an exemption.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder will be allowed as a refund or a credit against such non-U.S. holder's U.S. federal income tax liability, if any, provided that the required information is timely furnished to the IRS. Non-U.S. holders

should consult their own tax advisors regarding the filing of a U.S. tax return for claiming a refund of such backup withholding.

S-20

Table of Contents

Foreign Account Tax Compliance Act

Pursuant to Sections 1471 to 1474 of the Code and the Treasury regulations promulgated thereunder, or FATCA, dividends paid in respect of our common stock, and, after December 31, 2018, gross proceeds from the sale or other disposition of our common stock held by or through certain foreign financial institutions (as specially defined under the Code for purposes of these rules, including investment funds) will be subject to withholding at a rate of 30%, unless (1) such institution enters into an agreement with the Treasury to report, on an annual basis, information with respect to interests in, and accounts maintained by, the institution to the extent such interests or accounts are held by certain U.S. persons and by certain non-U.S. entities that are wholly or partially owned by U.S. persons and to withhold on certain payments or (2) such institution otherwise qualifies for an exemption from these rules. An intergovernmental agreement between the U.S. and an applicable foreign country, or future Treasury regulations or other guidance, may modify these requirements. Accordingly, the entity through which our common stock is held will affect the determination of whether such withholding is required. Similarly, dividends in respect of, and after December 31, 2018, gross proceeds from the sale of, our common stock held by an investor that is a non-financial foreign entity (as specially defined under the Code for purposes of these rules) that does not qualify under certain exemptions will be subject to withholding at a rate of 30%, unless such entity either (1) certifies to us that such entity does not have any substantial United States owners (as specifically defined under the Code for purposes of these rules) or provides certain information regarding the entity's substantial United States owners, which we will in turn provide to the IRS or (2) such non-financial foreign entity otherwise qualifies for an exemption from these rules. We will not pay any additional amounts to non-U.S. holders in respect of any amounts withheld. A foreign financial institution or non-financial foreign entity can generally meet the certification requirements by providing a properly executed applicable IRS Form W-8. Non-U.S. holders are encouraged to consult their tax advisors regarding the possible implications of FATCA on their investment in our common stock.

THE SUMMARY OF MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES ABOVE IS INCLUDED FOR GENERAL INFORMATION PURPOSES ONLY AND IS NOT TAX ADVICE. POTENTIAL PURCHASERS OF OUR COMMON STOCK ARE URGED TO CONSULT THEIR TAX ADVISORS TO DETERMINE THE U.S. FEDERAL, STATE, LOCAL AND FOREIGN TAX CONSIDERATIONS OF PURCHASING, OWNING AND DISPOSING OF OUR COMMON STOCK.

Table of Contents**UNDERWRITING**

We are offering the shares of common stock described in this prospectus supplement through the several underwriters named in the table below. Goldman Sachs & Co. LLC, J.P. Morgan Securities LLC and Leerink Partners LLC are acting as representatives of the several underwriters listed below. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus supplement, the number of shares of common stock listed next to its name in the following table:

Name	Number of Shares
Goldman Sachs & Co. LLC	1,923,077
J.P. Morgan Securities LLC	1,923,077
Leerink Partners LLC	1,025,641
Wells Fargo Securities, LLC	256,410
Total	5,128,205

The underwriters are committed to purchase all the shares offered by us if they purchase any shares. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated. We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

The underwriters propose to offer the common shares directly to the public at the initial public offering price set forth on the cover page of this prospectus supplement and to certain dealers at that price less a concession not in excess of \$0.702 per share. After the initial offering of the shares to the public, the offering price and other selling terms may be changed by the underwriters. 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.

Option to Purchase Additional Shares

The underwriters have an option to buy up to 769,230 additional shares of common stock from us to cover sales of shares by the underwriters which exceed the number of shares specified in the table above. The underwriters have 30 days from the date of this prospectus supplement to exercise this option to purchase additional shares. If any shares are purchased with this option to purchase additional shares, the underwriters will purchase shares in approximately the same proportion as shown in the table above. If any additional shares of common stock are purchased, the underwriters will offer the additional shares on the same terms as those on which the shares are being offered.

Table of Contents**Discounts and Commissions**

The underwriting fee is equal to the public offering price per share of common stock less the amount paid by the underwriters to us per share of common stock. The underwriting fee is \$1.17 per share. The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Without option to purchase additional shares exercised	With full option to purchase additional shares exercised
Per Share	\$ 1.17	\$ 1.17
Total	\$ 6,000,000	\$ 6,899,999

In addition, we have agreed to pay Wells Fargo Securities, LLC, one of the underwriters in this offering, structuring fees of \$250,000. We estimate that our total expenses of this offering, excluding the underwriting discounts and commissions and the structuring fees, will be approximately \$275,000.

A prospectus supplement in electronic format may be made available on the websites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

No Sale of Similar Securities

We have agreed that we will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any shares of our common stock or securities convertible into or exchangeable or exercisable for any shares of our common stock, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other agreement that transfers all or a portion of the economic consequences associated with the ownership of any shares of common stock or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of shares of common stock or such other securities, in cash or otherwise), in each case without the prior written consent of the representatives for a period of 90 days after the date of this prospectus supplement. Notwithstanding these restrictions, we may: (A) effect the sale of the shares contemplated by this prospectus supplement; (B) issue shares of our common stock or options to purchase common stock, or issue shares of common stock upon exercise of options, in each case pursuant to any stock option, stock bonus or other stock plan or arrangement described in the registration statement or this prospectus supplement; *provided* that, if the holder of any such common stock or other securities is a director or executive officer referred to in the paragraph below, any securities acquired will remain subject to the restrictions set forth in the paragraph below; (C) withhold and cancel shares of our common stock released upon vesting of restricted stock awards granted pursuant to any restricted stock agreement, stock bonus or other stock plan or arrangement described in the registration statement or this prospectus supplement in order to pay withholding taxes to tax authorities on behalf of the recipient of any such restricted stock award, and (D) issue (or agree to issue) shares of common stock or related securities (as defined below) in connection

with a licensing arrangement, joint venture, acquisition or business combination or other collaboration or strategic transaction; *provided* that, in the case of clause (D), recipients of such common stock or related securities agree to be bound by the terms of the lock-up described in the paragraph below applicable to our directors and executive officers and the sum of the aggregate number of shares of common stock or related securities so issued shall not exceed 5% of the total outstanding shares of our common stock prior to giving effect to the sale of the shares offered by this prospectus

S-23

Table of Contents

supplement. For purposes of the foregoing, related securities shall mean any options or warrants or other rights to acquire common stock or any securities exchangeable or exercisable for or convertible into common stock, or to acquire other securities or rights ultimately exchangeable or exercisable for, or convertible into, our common stock.

Our directors and executive officers have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant to which each of these persons, for a period of 90 days after the date of this prospectus supplement, may not, without the prior written consent of the representatives on behalf of the underwriters, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock or any securities convertible into or exercisable or exchangeable for our common stock (including, without limitation, common stock or such other securities which may be deemed to be beneficially owned by such directors, executive officers, managers and members in accordance with the rules and regulations of the SEC and securities which may be issued upon exercise of a stock option or warrant) or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock or such other securities, in cash or otherwise, or (3) make any demand for or exercise any right with respect to the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock, in each case other than: (A) transfers of shares of our common stock or options or other rights to acquire shares of our common stock as a bona fide gift; (B) distributions of shares of our common stock to members or stockholders of the undersigned; (C) transfers of shares of our common stock or options or other rights to acquire shares of our common stock pursuant to a qualified domestic relations order or a negotiated divorce settlement; and (D) transfer or surrender for cancellation of shares of our common stock to us upon the vesting of restricted shares of common stock to cover tax withholding obligations in connection with such vesting pursuant to a restricted stock agreement, stock bonus or other stock plan or arrangement existing as of the date hereof and described in our public filings with the SEC, and any remaining shares of common stock acquired upon such vesting shall remain subject to the restrictions described in this paragraph; *provided* that in the case of any transfer or distribution pursuant to clause (A), (B), or (C), each donee or distributee shall execute and deliver to the representatives a lock-up letter in the form of set forth in this paragraph; and *provided, further*, that in the case of any transfer or distribution pursuant to clause (A), (B) or (C), no filing by any party (donor, donee, transferor or transferee) under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with such transfer or distribution (other than a filing on a Form 5 made after the expiration of the 90-day period referred to above unless such Form 5 is required to be filed during such period). In addition, our directors and executive officers may (1) sell shares of our common stock pursuant to a trading plan established pursuant to Rule 10b5-1 under the Exchange Act, or a 10b5-1 plan, existing on the date hereof and disclosed to the representatives and (2) enter into a 10b5-1 plan during the 90 day period; *provided that* in the case of any sales pursuant to (1), each filing with the SEC shall indicate that the sale was made pursuant to an existing 10b5-1 plan and, in the case of (2), such 10b5-1 plan does not allow for any sales during the 90-day period and no filing under the Exchange Act or other public announcement shall be required or shall be made voluntarily in connection with the establishment of such 10b5-1 plan.

Other Relationships

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.

S-24

Table of Contents

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 trade 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 assets, securities and/or instruments of ours (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.

Stabilization and Short Positions

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of the common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered shorts, which are short positions in an amount not greater than the underwriters' option to purchase additional shares referred to above, or may be naked shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. 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 that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act of 1933, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the common stock or preventing or retarding a decline in the market price of the common stock, and, as a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The Nasdaq Global Select Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering certain of the underwriters (and selling group members) may engage in passive market making transactions in our common stock on The Nasdaq Stock Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The Nasdaq Stock Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of

these transactions. If passive market making is commenced, it may be discontinued at any time.

S-25

Table of Contents

Sales Outside of the United States

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus supplement in any jurisdiction where action for that purpose is required. The securities offered by this prospectus supplement may not be offered or sold, directly or indirectly, nor may this prospectus supplement or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus supplement comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus supplement. This prospectus supplement does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus supplement in any jurisdiction in which such an offer or a solicitation is unlawful.

Selling Restrictions

Notice to Prospective Investors in the 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, with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, no offer of shares of our common stock may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- B. 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 underwriters; or
- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive and each person who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and us that it is a qualified investor within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive.

In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an offer of shares to the public in relation to any shares in any Relevant Member State means the communication in any form and by means of sufficient information on the terms of

the offer and the shares to be offered so as to enable an investor to decide to purchase 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.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this prospectus supplement is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are qualified investors (as

Table of Contents

defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order, all such persons together being referred to as relevant persons, or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this prospectus supplement or the accompanying prospectus or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this prospectus supplement or the accompanying prospectus relates to may be made or taken exclusively by relevant persons.

Notice to Prospective Investors in Canada

The shares may be sold 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 shares 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 supplement (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 for particulars 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.

Notice to Prospective Investors in Hong Kong

The shares may not be offered or sold 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 Ordinance (Cap.32, Laws of Hong Kong), or (ii) to professional investors within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a prospectus within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), 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 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 within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Singapore

Neither this prospectus supplement nor the accompanying prospectus has been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, neither this prospectus supplement, the accompanying prospectus nor any other document or material in connection with the offer or sale, or invitation for subscription

S-27

Table of Contents

or purchase, of the shares may 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 under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person, or any person pursuant to Section 275(1A), 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.

Where the shares are subscribed or purchased under Section 275 by a relevant person which is: (a) a corporation (which is not an accredited investor), 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; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the shares under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Notice to Prospective Investors in Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan, or the Financial Instruments and Exchange Law, and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Table of Contents

LEGAL MATTERS

Certain legal matters relating to the issuance of the shares offered by this prospectus supplement will be passed upon for us by Cooley LLP, Palo Alto, California. Davis Polk & Wardwell LLP, Menlo Park, California, is counsel to the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, an independent registered public accounting firm, has audited our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016, and the effectiveness of our internal control over financial reporting as of December 31, 2016, as set forth in their reports, which are incorporated by reference in this prospectus supplement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are currently subject to the reporting requirements of the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. You may read and copy (at prescribed rates) any such reports, proxy statements and other information at the SEC's Public Reference Room at 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. Our SEC filings are also available to you on the SEC's website at www.sec.gov and in the Investors section of our website at www.fiveprime.com. Our website and the information contained on, or accessible through, our website, are not incorporated into and are not a part of this prospectus supplement or the accompanying prospectus.

This prospectus supplement and accompanying prospectus are part of a registration statement on Form S-3 we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Statements in this prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

Table of Contents

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC's rules allow us to incorporate by reference information into this prospectus supplement and the accompanying prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The SEC file number for the documents incorporated by reference in this prospectus is 001-36070. We incorporate by reference the documents listed below and any future information filed with the SEC under Sections 13(a), 13(c), 14, or 15(d) of the Exchange Act between the date of this prospectus supplement and the termination of this offering; provided, however, that we are not incorporating any information furnished under Item 2.02 or Item 7.01 of any Current Report on Form 8-K:

our Annual Report on Form 10-K for the year ended December 31, 2016, which was filed with the SEC on February 24, 2017;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2016 from our definitive proxy statement relating to our 2017 annual meeting of stockholders, which was filed with the SEC on March 31, 2017;

our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2017, June 30, 2017 and September 30, 2017, which were filed with the SEC on May 5, 2017, August 8, 2017 and November 6, 2017, respectively;

our Current Reports on Form 8-K, which were filed with the SEC on February 13, 2017, March 20, 2017, May 4, 2017, May 12, 2017, May 15, 2017, June 21, 2017, August 25, 2017, August 28, 2017, October 23, 2017, November 8, 2017, November 22, 2017, December 19, 2017 and January 23, 2018; and our Current Report on Form 8-K/A, which was filed on August 24, 2017; and

the description of our common stock contained in our registration statement on Form 8-A, which was filed on September 16, 2013, including any amendments or reports filed for the purpose of updating the description.

Any statement contained in a document incorporated by reference in this prospectus supplement shall be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or in any other subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus supplement modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement.

You may obtain copies of any of these filings by contacting us at the address and telephone number indicated below or by contacting the SEC as described above in the section titled "Where You Can Find More Information." Documents incorporated by reference are available from us without charge, excluding all exhibits unless an exhibit has been specifically incorporated by reference into this prospectus supplement, by requesting them in writing or by telephone at:

Edgar Filing: FIVE PRIME THERAPEUTICS INC - Form 424B5

Five Prime Therapeutics, Inc.

Attention: Investor Relations

111 Oyster Point Boulevard

South San Francisco, California 94080

(415) 365-5737

S-30

Table of Contents

PROSPECTUS

Common Stock

From time to time, we may offer and sell shares of our common stock described in this prospectus.

We will provide the specific terms of these offerings in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as the documents incorporated by reference, before buying any of the common stock being offered.

Our common stock is listed on The NASDAQ Global Select Market under the symbol FPRX. As of November 1, 2016, the closing price of our common stock was \$48.94.

Investing in our common stock involves risks. You should review carefully the risks and uncertainties described under the heading Risk Factors contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering and under similar headings in the documents that are incorporated by reference into this prospectus.

This prospectus may not be used to offer or sell any common stock unless accompanied by a prospectus supplement.

We may sell shares of common stock directly to investors, to or through one or more underwriters, dealers and agents, or through a combination of these methods, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section titled Plan of Distribution in this prospectus. If any underwriters, dealers or agents are involved in the sale of our common stock, their names and any applicable purchase price, fee, commission or discount arrangement between or among them, and any applicable over-allotment options or any other options, will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement.

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 November 3, 2016.

Table of Contents

TABLE OF CONTENTS

	<u>Page</u>
<u>ABOUT THIS PROSPECTUS</u>	i
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	2
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	3
<u>USE OF PROCEEDS</u>	5
<u>DESCRIPTION OF COMMON STOCK</u>	6
<u>PLAN OF DISTRIBUTION</u>	10
<u>LEGAL MATTERS</u>	12
<u>EXPERTS</u>	12
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	12
<u>INCORPORATION OF CERTAIN INFORMATION BY REFERENCE</u>	12

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the U.S. Securities and Exchange Commission, or the SEC, using a shelf registration process. Under this shelf registration process, we may offer and sell shares of our common stock in one or more offerings. There is no limit on the aggregate amount of common stock that we may offer pursuant to the registration statement of which this prospectus is a part. This prospectus provides you with a general description of the common stock we may offer.

Each time that we offer shares of our common stock under this prospectus, we will provide a supplement to this prospectus that contains specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change any of the information contained in this prospectus or in the documents that we have incorporated by reference into this prospectus. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you should rely on the prospectus supplement. We urge you to read carefully this prospectus, any applicable prospectus supplement and any free writing prospectuses we have authorized for use in connection with a specific offering, together with the information incorporated herein by reference as described in the section titled **Incorporation of Certain Information by Reference**, before purchasing the common stock being offered.

This prospectus may not be used to offer or sell any common stock unless it is accompanied by a prospectus supplement.

You should rely only on the information contained in, or incorporated by reference into, this prospectus and the applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different or additional information. This prospectus is an offer to sell only the common stock offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so.

The information appearing in this prospectus, any applicable prospectus supplement and any related free writing prospectus is accurate only as of the date on the front of the document, and any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus, the applicable prospectus supplement or any related free writing prospectus, or any sale of common stock. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or have been or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described in the section titled **Where You Can Find More Information**.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus to **Five Prime**, the company, **we**, **us**, **our** and similar references refer to Five Prime Therapeutics, Inc. The Five Prime logo and RIPPS® are our registered trademarks. This prospectus also contains registered marks, trademarks and trade names of other companies. All other trademarks, registered marks and trade names appearing in this prospectus are the property of their respective holders.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our common stock discussed under the heading Risk Factors contained in the applicable prospectus supplement, any related free writing prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Our Company

We are a clinical-stage biotechnology company focused on discovering and developing innovative protein therapeutics to improve the lives of patients with serious diseases. We currently have three product candidates in clinical development covering multiple potential indications. Each of our product candidates has an innovative mechanism of action and addresses patient populations for which better therapies are still needed. We have an emphasis in immuno-oncology, an area in which we have clinical and discovery programs and product and discovery collaborations. In addition, we plan to use companion diagnostics, where appropriate, for our clinical programs to allow us to select patients most likely to benefit from treatment.

Cabiralizumab (FPA008) is an antibody that inhibits colony stimulating factor-1 that we are studying in clinical trials as a monotherapy in pigmented villonodular synovitis and in multiple cancers in combination with Bristol-Myers Squibb Company's PD-1 immune checkpoint inhibitor, *Opdivo*® (nivolumab). In October 2015, we entered into a license and collaboration agreement with Bristol-Myers Squibb Company, or BMS, pursuant to which we granted BMS an exclusive worldwide license for the development and commercialization of cabiralizumab.

FPA144 is an antibody that inhibits fibroblast growth factor receptor 2b that we are developing to treat patients with gastric (stomach) cancer and is in a Phase 1 clinical trial.

FP-1039 is a fusion protein that traps and neutralizes cancer-promoting fibroblast growth factors involved in cancer cell proliferation and new blood vessel formation, which is in Phase 1b clinical development to treat patients with malignant pleural mesothelioma.

We have a differentiated target discovery platform and library, which we believe encompasses substantially all of the body's medically important targets for protein therapeutics. We have identified approximately 700 of these proteins, which we refer to as the immunome, that we believe modulate immune cell interactions and may be important in understanding and treating cancer patients using immuno-oncology therapeutics. Our target discovery platform and capabilities uniquely position us to explore pathways in cancer and inflammation and their intersection in immuno-oncology, an area of oncology with significant therapeutic potential and the focus of our research activities. We are applying all aspects of our biologics discovery platform, including cell-based screening, in vivo screening, receptor-ligand matching technologies and bioinformatics, in our immuno-oncology research program. We have identified several targets that we believe could be useful in immuno-oncology and are actively validating these and looking for additional targets. We generate and preclinically test protein therapeutics, including antibodies and ligand

traps, containing or directed to the targets we identify. We plan to advance selected therapeutic candidates into clinical development, with a goal of filing at least one Investigational New Drug application for a new molecule per year for the foreseeable future, beginning in 2017.

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks and uncertainties described under the heading **Risk Factors** contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section titled **Risk Factors** contained in our most recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with a specific offering. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also carefully read the section titled **Special Note Regarding Forward-Looking Statements**.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the documents incorporated by reference herein and therein, and any free writing prospectus that we have authorized for use in connection with this offering, contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that involve substantial risks and uncertainties. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

our estimates regarding our expenses, revenues, anticipated capital requirements and our needs for additional financing;

our receipt of future milestone payments and/or royalties, and the timing of such payments;

our or our partners' ability to timely advance drug candidates into and through clinical data readouts and successful completion of clinical trials;

the timing of the initiation, progress and results of preclinical studies and research and development programs;

our expectations regarding the potential safety, efficacy or clinical utility of our product candidates;

the implementation, timing and likelihood of success of our plans to develop companion diagnostics for our product candidates;

our ability to establish and maintain collaborations and necessary licenses;

the implementation of our business model and strategic plans for our business, drug candidates and technology;

the scope of protection we establish and maintain for intellectual property rights covering our drug candidates and technology;

the size of patient populations targeted by products we or our partners develop and market adoption of our potential products by physicians and patients;

the timing or likelihood of regulatory filings and approvals;

the ability to negotiate adequate reimbursement and pricing for our drug candidates by third parties and government authorities;

developments relating to our competitors and our industry; and

our expectations regarding licensing, acquisitions and strategic operations.

In some cases, you can identify forward-looking statements by terms such as anticipates, believes, could, estimates, expects, may, plans, potential, predicts, projects, should, would, will and similar expressions intended to identify forward-looking statements. These statements, which reflect our current views with respect to future events, are based on assumptions and are subject to risks and uncertainties. Given these risks and uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail, and incorporate by reference into this prospectus in their entirety, many of these risks and uncertainties under the heading Risk Factors contained in the applicable prospectus supplement, in any free writing prospectus we may authorize for use in connection with a specific offering, and in our most recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

Table of Contents

Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. You should read this prospectus, the applicable prospectus supplement, together with the documents we have filed with the SEC that are incorporated by reference, and any free writing prospectus we have authorized for use in connection with a specific offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

Table of Contents

USE OF PROCEEDS

Unless otherwise indicated in any prospectus supplement or free writing prospectus, the net proceeds from the sale of our common stock offered by this prospectus will be used for general corporate purposes and working capital requirements. As a result, unless otherwise indicated in the prospectus supplement, our management will have broad discretion to allocate the net proceeds of the offerings. Pending their ultimate use, we intend to invest the net proceeds in a variety of securities, including commercial paper, government and non-government debt securities and/or money market funds that invest in such securities.

Table of Contents

DESCRIPTION OF COMMON STOCK

The following describes the common stock that we may offer under this prospectus, including the material provisions of our amended and restated certificate of incorporation and our amended and restated bylaws, the registration rights agreement to which we and certain of our stockholders are parties and certain provisions of the General Corporation Law of the State of Delaware, or the DGCL. Because the following is only a summary, it does not contain all of the information that may be important to you. For a complete description, you should refer to our amended and restated certificate of incorporation, amended and restated bylaws and registration rights agreement, copies of which have been filed with the SEC. See the sections of this prospectus titled *Where You Can Find More Information* and *Incorporation of Certain Information by Reference*.

General

Our amended and restated certificate of incorporation authorizes us to issue up to 100,000,000 shares of common stock, \$0.001 par value, and 10,000,000 shares of preferred stock, \$0.001 par value. As of September 30, 2016, there were:

28,417,589 shares of common stock issued and outstanding; and

3,475,558 shares of common stock issuable upon exercise of outstanding options.

As of September 30, 2016, we had 41 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Common Stock

Voting Rights. Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders. The affirmative vote of holders of substantially 66% of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, will be required to amend certain provisions of our amended and restated certificate of incorporation, including provisions relating to amending our amended and restated bylaws, the classified board, the size of our board, removal of directors, director liability, vacancies on our board, special meetings, stockholder notices, actions by written consent and exclusive jurisdiction.

Dividends. Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose.

Liquidation. In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any outstanding preferred stock.

Rights and Preferences. Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders

of shares of any series of our preferred stock that we may designate in the future.

Fully Paid and Nonassessable. All outstanding shares of our common stock are fully paid and non-assessable, and the shares of common stock to be issued upon completion of this offering will be fully paid and non-assessable.

Table of Contents

Registration Rights

Holders of 1,212,388 shares of our common stock have the right to demand that we file a registration statement or request that we cover their shares by a registration statement that we otherwise file, as described below.

Demand Registration Rights

The holders of a majority of the shares having demand registration rights may request that we register all or a portion of their shares of common stock for sale under the Securities Act. We will effect the registration as requested, unless, in the good faith judgment of our board of directors, such registration would be materially detrimental to the company and its stockholders and should be delayed. In addition, holders of the shares having demand registration rights may make unlimited requests that we register all or a portion of their common stock for sale under the Securities Act on Form S-3, or any successor form, so long as the aggregate price to the public in connection with any such offering is at least \$1 million.

Incidental Registration Rights

In addition, if at any time we register any shares of our common stock, the holders of all shares having piggyback registration rights are entitled to notice of the registration and to include all or a portion of their shares of common stock in the registration.

Other Provisions

In the event that any registration in which the holders of registrable shares participate pursuant to the registration rights agreement is an underwritten public offering, the number of registrable shares to be included may, in specified circumstances, be limited due to market conditions.

For certain of these holders, we will pay all registration expenses, other than underwriting discounts and selling commissions, and the reasonable fees and expenses of a single special counsel for the selling stockholders related to any demand, piggyback and Form S-3 registration. The registration rights agreement contains customary cross-indemnification provisions, pursuant to which we must indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us, and they must indemnify us for material misstatements or omissions in the registration statement attributable to them. The demand, piggyback and Form S-3 registration rights described above will expire with respect to a majority of the shares having registration rights on September 23, 2017.

Anti-Takeover Provisions

Our Certificate of Incorporation and Bylaws

Our amended and restated certificate of incorporation and amended and restated bylaws include a number of provisions that may deter or impede unsolicited or hostile takeovers or changes of control or management. These provisions include:

Issuance of undesignated preferred stock. Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and

preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock enables our board of directors to make it more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

Table of Contents

Classified board. Our amended and restated certificate of incorporation provides for a classified board of directors consisting of three classes of directors, with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. This provision may have the effect of delaying a change in control of our board.

Board of directors vacancies. Our amended and restated certificate of incorporation and amended and restated bylaws authorize only our board of directors to fill vacant directorships. In addition, the number of directors constituting our board of directors may be set only by resolution adopted by a majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and gaining control of our board of directors by filling the resulting vacancies with its own nominees.

Stockholder action; special meetings of stockholders. Our amended and restated certificate of incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. Stockholders will not be permitted to cumulate their votes for the election of directors. Our amended and restated certificate of incorporation further provides that only the chairman of our board of directors or a majority of our board of directors may call special meetings of our stockholders.

Advance notice requirements for stockholder proposals and director nominations. Our amended and restated bylaws provide advance notice procedures for stockholders seeking to bring business before our annual meeting of stockholders or to nominate candidates for election as directors at our annual meeting of stockholders. Our amended and restated bylaws also specify certain requirements as to the form and content of a stockholder's notice. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at annual meetings of stockholders.

We designed these provisions to enhance the likelihood of continued stability in the composition of our board of directors and its policies, to discourage certain types of transactions that may involve an actual or threatened acquisition of us, and to reduce our vulnerability to an unsolicited acquisition proposal. We also designed these provisions to discourage certain tactics that may be used in proxy fights. However, these provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they may also reduce fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Section 203 of the General Corporation Law of the State of Delaware

We are subject to Section 203 of the DGCL, which prohibits a Delaware corporation from engaging in a business combination with any interested stockholder for a period of three years following the date the person became an interested stockholder, with the following exceptions:

before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested holder;

upon completion 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 began, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (a) by persons who are directors and also officers and (b) pursuant to employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; and

Table of Contents

on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines business combination to include the following:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an interested stockholder as an entity or person who, together with such entity's or person's affiliates and associates, beneficially owns, or is an affiliate of the corporation and within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

A Delaware corporation may opt out of these provisions with an express provision in its certificate of incorporation. We have not opted out of these provisions, which may as a result discourage or prevent mergers or other takeover or change of control attempts of us.

Choice of Forum

Our amended and restated certificate of incorporation provides that unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a breach of fiduciary duty owed by, or other wrongdoing by, any director, officer, employee or agent to us or our stockholders, (3) any action asserting a claim against us arising pursuant to the DGCL or our certificate of incorporation or bylaws, (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws, or (5) any action asserting a claim against us that is governed by the internal affairs doctrine.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Listing

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

Table of Contents

PLAN OF DISTRIBUTION

We may sell our common stock from time to time pursuant to underwritten public offerings, at-the-market offerings, negotiated transactions, block trades or a combination of these methods. We may sell the common stock to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute the common stock from time to time in one or more transactions:

at a fixed price or prices, which may be changed;

at market prices prevailing at the time of sale;

at prices related to such prevailing market prices; or

at negotiated prices.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the common stock, including, to the extent applicable:

the name or names of the underwriters, if any;

the purchase price of the common stock or other consideration therefor, and the proceeds, if any, we will receive from the sale;

any agency fees or underwriting discounts and other items constituting agents or underwriters compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchange or market on which the common stock may be listed.

Only underwriters named in the prospectus supplement will be underwriters of the common stock offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the common stock for their own account and may resell the common stock from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the common stock will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the common stock to the public through

underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the common stock offered by the prospectus supplement, other than the common stock covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell the common stock directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of the common stock and we will describe any commissions payable to the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, the agent will act on a best-efforts basis for the period of its appointment.

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

Table of Contents

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the common stock, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the common stock originally sold by the dealer is purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the common stock to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters that are qualified market makers on The NASDAQ Global Select Market may engage in passive market making transactions in the common stock on The NASDAQ Global Select Market in accordance with Regulation M under the Exchange Act during the business day prior to the pricing of the offering or before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the common stock at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

In compliance with guidelines of the Financial Industry Regulatory Authority, or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the common stock offered pursuant to this prospectus and the applicable prospectus supplement.

Table of Contents

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the legal validity of the common stock offered by this prospectus will be passed upon for us by Cooley LLP, Palo Alto, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2015, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth or incorporated by reference in the registration statement. Whenever a reference is made in this prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference into this prospectus for a copy of such contract, agreement or other document. We are currently subject to the reporting requirements of the Exchange Act, and in accordance therewith file periodic reports, proxy statements and other information with the SEC. You may read and copy (at prescribed rates) any such reports, proxy statements and other information at the SEC's Public Reference Room at 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. Our SEC filings are also available to you on the SEC's website at www.sec.gov and in the Investors section of our website at www.fiveprime.com. Our website and the information contained on that site, or connected to that site, are not incorporated into and are not a part of this prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC's rules allow us to incorporate by reference information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act until we file a post-effective amendment that indicates the termination of the offering of the common stock made by this prospectus and will become a part of this prospectus from the date that such documents are filed with the SEC. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed filed with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

Table of Contents

We incorporate by reference into this prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 001-36070):

our Annual Report on Form 10-K for the year ended December 31, 2015, which was filed with the SEC on March 11, 2016;

the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2015 from our definitive proxy statement relating to our 2016 annual meeting of stockholders, which was filed with the SEC on March 30, 2016;

our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2016 and June 30, 2016, which were filed with the SEC on May 6, 2016 and August 5, 2016, respectively;

our Current Reports on Form 8-K, which were filed with the SEC on January 11, 2016, January 19, 2016, January 20, 2016, January 21, 2016, January 25, 2016, March 10, 2016, March 16, 2016, May 20, 2016 (two reports), June 6, 2016 (two reports) and September 14, 2016; and

the description of our common stock contained in our registration statement on Form 8-A, which was filed on September 16, 2013, including any amendments or reports filed for the purpose of updating the description.

Any statement contained in a document incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or in any other subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

You may obtain copies of any of these filings by contacting us at the address and telephone number indicated below or by contacting the SEC as described above in the section titled **Where You Can Find More Information**. Documents incorporated by reference are available from us without charge, excluding all exhibits unless an exhibit has been specifically incorporated by reference into this prospectus, by requesting them in writing or by telephone at:

Five Prime Therapeutics, Inc.

Attention: Investor Relations

Two Corporate Drive

South San Francisco, California 94080

(415) 365-5737

Table of Contents

5,128,205 Shares

Common Stock

PROSPECTUS SUPPLEMENT

Goldman Sachs & Co. LLC

J.P. Morgan

Leerink Partners

Wells Fargo Securities

January 24, 2018